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Original Communications

CONGENITAL MEDIAL SCLEROSIS OF THE CORONARY ARTERY*

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THAT medial sclerosis was to be clearly differentiated from atheromatosis of the intima, was recognized by Virchow,[1, 2] who described it as most frequently found in the peripheral arteries; but nevertheless it was included in the description of arteriosclerosis by Oberndorfer,[3] Jores,[4] Aschoff,[5] Kaufmann,[6] and Saltykow.[7] However, it was Mönckeberg[8, 9, 10] and Marchand,[11] who emphasized pure calcification of the media as an independent condition. These changes were also found to be present in the large arteries and coronaries, even in infants following infection.[12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24] The literature on the occurrence of spontaneous arteriosclerotic changes in the arteries of rabbits has been summarized by Newburgh and Clarkson,[25] and by Nuzum, Elliot, Evans, and Priest,[26] who described one type consisting of necrosis and calcification which appeared to affect the media. In the attempt to produce experimental arteriosclerosis, changes in the media have been reported by numerous workers using various methods, such as high protein and fat diets, adrenalin, pituitrin, cholesterol, uranium, alcohol and potassium iodide;[25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 66] also the discovery of irradiated ergosterol was soon followed by the description of medial calcification in animals after administration of large doses of this substance.[43, 44, 45, 46, 47, 48, 49, 50, 67] Pathological changes such as these have been reported in infants and newborn babies,[18, 19, 51, 52, 53] and some of them bear a sufficiently close similarity to the case herein reported to warrant reviewing.

McMicheal[52] described the case of a child eighteen months old, dying of thrombosis of the superior mesenteric artery, who also showed fibrous

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changes in the coronary arteries of the heart. This case was a gentile; family history including Wassermann reactions of both parents was negative. The infant had had no previous illness, and the terminal illness was ushered in by fever and mild gastrointestinal disturbance. At autopsy the heart was not found to be enlarged, but the coronaries were thickened and dense. Upon section they showed great connective tissue proliferation external to the elastic lamina with narrowing of the lumen; this condition was not present in the smaller arterioles. In the heart wall there was a loss of muscle tissue with replacement by fibrous tissue. Thrombo-angiitis obliterans and periarteritis nodosa were excluded because of the complete absence of any involvement of the adventitia. Although there was evidence of tuberculous infection in this case, it was not considered as an etiological factor, and the process was regarded as an endarteritis due to acute or subacute infection of an unknown nature.

Hughes and Perry[53] report a case of a child seven weeks old who died suddenly and at autopsy revealed marked thickening and tortuosity of the coronary arteries, while the rest of the heart appeared normal. There was intimal thickening composed of loosely arranged fibrous connective tissue, and the media was almost completely calcified, with only very broken fragments of muscle fibers, while the adventitia showed some increase in fibrous tissue. This change was also confined to the large arteries, while the arterioles were normal. The family history was negative, except for an attack of influenza in the mother during her pregnancy. Her Wassermann reaction was negative. Our opinion is that this was a case of primary pathology in the media, probably due to intrauterine influenza, similar to those cases reported by Wiesel.[20, 21, 22, 23, 24] Durante's[51] case was a premature child, fifteen days old, who died of acute peritonitis following an umbilical infection. The etiology in this case cannot be determined because of the lack of information regarding the parents, but syphilis, tuberculosis or alcohol might be factors. Histological examination revealed the myocardium to be normal, but there were lesions of all degrees, from granular degeneration to well-formed calcareous plaque, in the inner third of the media of the pulmonary artery. The external tunic was normal and the internal tunic probably became detached spontaneously after death. In the less severely affected regions there was a granular condition of the tissue, the cells of which stained diffusely and were less clearly separated from each other. The nuclei stained well but a granular substance deposited in the protoplasm or in the interstitial tissue masked the outline of these cells which appeared to be degenerating and had lost some of their affinity for stains. At the points where the lesion was more advanced, the tissue was infiltrated with masses which had an irregular outline and either remained unstained or were stained pale yellow with picrocarmine, and dark violet with hematoxylin, and

yellow with picric acid. These masses were insoluble in ether and in some places replaced the muscle cells. It was impossible to determine whether they were due to a transformation of the cellular elements or whether they had been deposited between the cells, although Durante is inclined to the latter hypothesis. In the slightly affected regions the lesion was clearly limited to the internal third of the media, and at the points at which the lesion reached and projected into the interior of the vessel, the intima was always intact and at no point were there any traces of rupture. The aorta showed similar changes. Our opinion is that this is a case of primary medial calcification or hyalinization of doubtful etiology.

Surbek[18] reports an autopsy of a newborn infant three days old, in which were found, as a result of an intrauterine diplococcal infection, fresh fibrinous pericarditis, acute splenic tumor and nephritis with chronic foci of inflammation. The mother had a chronic otitis media with an acute exacerbation; her Wassermann reaction was negative, and no spirochetes could be demonstrated in the child's liver. There was an extensive calcification of numerous organs with a predilection for the arteries. These changes found in the arteries may be summarized as a high degree of calcification of the media with formation of granulation and connective tissue in the region of the calcareous focus, chronic inflammatory infiltration in the adventitia and localized compensatory intimal proliferation without intimal degeneration. There were no inflammatory or degenerative changes found in the media which were not associated with calcification. The inflammatory changes in the adventitia went parallel, in extent and intensity, with the calcification in the media, so that it cannot be stated whether they were the result of the medial calcification or the direct result of the infection. Surbek thinks that the first is more reasonable, and that the condition was due primarily to a disturbance of the calcium metabolism which was expressed in the calcification of the arteries and various organs.

The autopsy reported by Jaffé[19] was that of a boy two days old whose mother suffered from severe hydramnios during pregnancy, but nothing else of importance was given in the history. A study of the vessels revealed a necrotic process localized chiefly in the inner half of the media, and affecting chiefly its muscle fibers. The necrosis was associated with calcification. The elastic tissue within the foci was largely destroyed and partly calcified, while the elastic fibers of the surrounding region had lost their wavy appearance and were peculiarly straight. It is the opinion of Jaffé that the process in this case was chiefly a necrosis which had later undergone calcification, and that it is similar to the vascular affections occurring in the course of acute infections as described by Wiesel.[20, 21, 22, 23, 24] There was no involvement of the intima or adventitia in this case.

CASE REPORT

A newborn white gentile male, delivered by cesarean section, died at the age of three days, following intermittent attacks of cyanosis and apnea, during which oxygen and artificial respiration were employed. The family history as well as the Wassermann reactions of both the mother and the father was negative. There were no previous illnesses of the mother. At examination before death, marked cyanosis and moderate dyspnea with frequent periods of apnea were noted. The left border of the heart dullness was 3.5 cm. to the left of the midsternal line while the right was 3 cm. to the right. The heart rhythm was regular and the rate 140. The Wassermann reaction on the spinal fluid was negative. Teleroentgenogram revealed

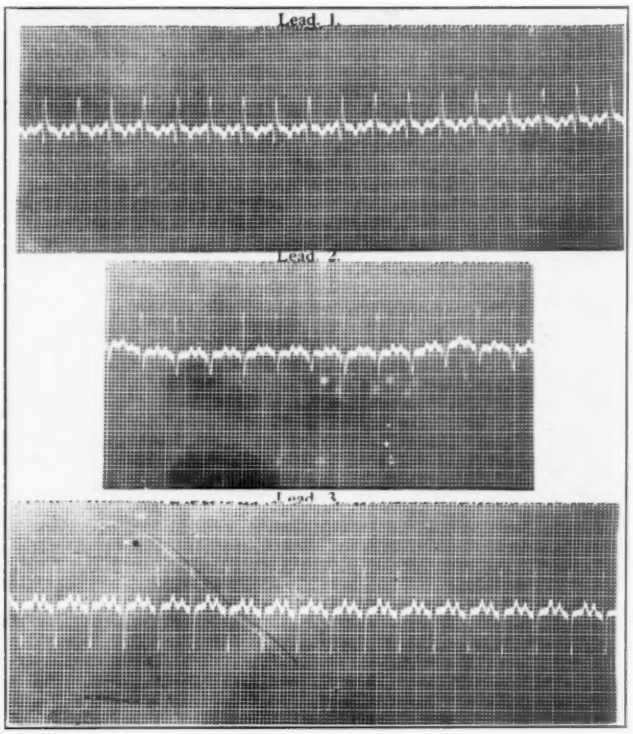

Fig. 1.—The R-T segment Lead I slightly convex followed by pointed inverted T-wave. The P-wave is also inverted, rate 166.

an inside chest diameter of 9.8 cm. with a transverse heart diameter of 6.4 cm. The electrocardiogram (Fig. 1) revealed a regular rhythm, rate 166, with inverted P- and T-waves in Lead I. The R-T interval in Lead I appears to be convex and followed by a pointed negative T-wave. At autopsy, eighteen hours after death, the body was found to be that of a well-developed, newborn male child. The body had not been embalmed but was well preserved on ice. There was a moderate amount of livor mortis but no evidence of rigor mortis. There were no malformations or other special marks of identification aside from the usual partially dried stump of the umbilical cord. Upon opening the body, no pathological changes were found in the abdominal cavity. In the thoracic cavity, scattered areas of petechial hemorrhage were found in the parietal pleura. The lungs were partially expanded and showed scattered areas of fresh hemorrhage into the lung parenchyma

Fig. 2.—The right anterior aspect of the heart showing the prominent, whitish and thickened right coronary artery.

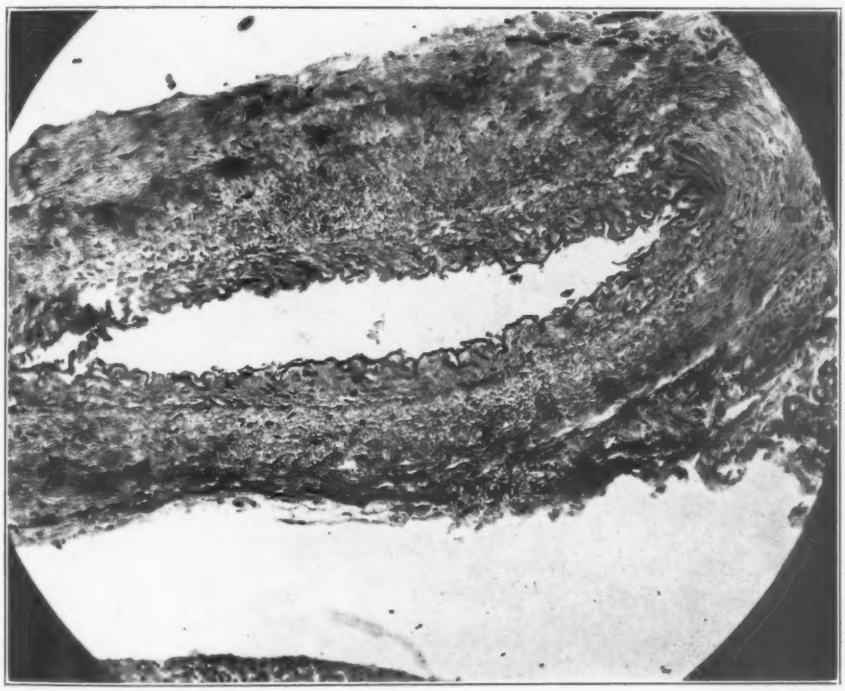

Fig. 3.—Low power view of one of the thickened coronary arteries. Note the normal lumen and tunica intima. The replacement of normal muscle by the connective tissue process in the media is present throughout the entire wall but is especially noticeable in the upper right portion.

and smaller bronchioles. The thymus was normal in size. The pericardial area was enlarged, measuring six and one-half centimeters in transverse diameter. Upon opening the pericardial sac it was found to be smooth, free from petechial hemorrhages and to contain the usual amount of clear fluid. Inspection of the heart in situ showed it to be slightly enlarged and to have an unusual degree of coronary prominence. The coronary arteries, especially the right, were opaque, white in color, almost cordlike, quite prominent but not tortuous. Upon palpation they were quite firm and cordlike (Fig. 2). Upon removal and opening the heart no abnormalities were found. The foramen ovale was closed. Cut section of the coronaries revealed no occlusion by thrombi or obliteration by intimal thickening. The intima upon gross examination was quite smooth and free from lipoid deposits or other evidence of thickening. The firmness and thickening appeared to be

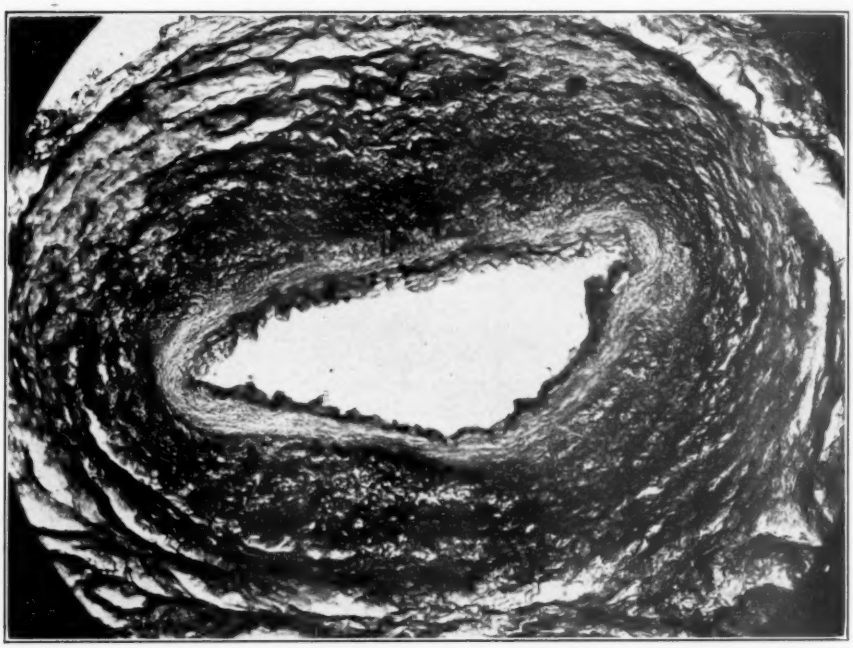

Fig. 4.—Picro-acid-fuchsin stain of the thickened coronary. Note the normal intimal layer, the marked connective tissue formation in the media and the normal adventitia.

within the medial layer of the arteries. The brain revealed no pathological changes and the cerebral arteries were entirely normal.

Microscopical sections prepared from the thickened coronary arteries and stained with eosin-hematoxylin and picro-acid-fuchsin stains showed definite changes in the medial layer. With the eosin-hematoxylin stains (Fig. 3) the endothelium could readily be identified and subendothelial tissue was lacking, while the inner elastic membrane was present throughout and was folded in the usual manner by the post-mortem contraction of the vessel. The tunica intima was therefore considered normal, showing no thickening or deposits, and the lumen was open and normal. In the medial layer the muscle cells could be easily identified just external to the inner elastic membrane, but passed rather abruptly into a zone of poorly staining, almost hyaline-like degeneration, which zone produced the great thickening noted in the gross specimen. The tunica externa was normal, and in none of the sections could evidence of cellular infiltration or of infection be found. The sec-

tions stained with the piero-acid-fuchsin (Fig. 4) also revealed the intimal layer to be entirely normal, but within the medial layer definite changes were noted. The circular and oblique muscles of the tunica media were present throughout in a thin layer immediately external to the inner elastic membrane, staining a pure yellow. The external portion of this thin muscle layer was invaded to an abnormal extent by red staining connective tissue, which formed a zone corresponding to the poorly stained zone above described external to the muscle. This zone of connective tissue was approximately twice as thick as the muscle layer and was entirely lacking in the sections of normal coronary arteries examined. There was no evidence of calcification within this zone. The tunica externa formed a

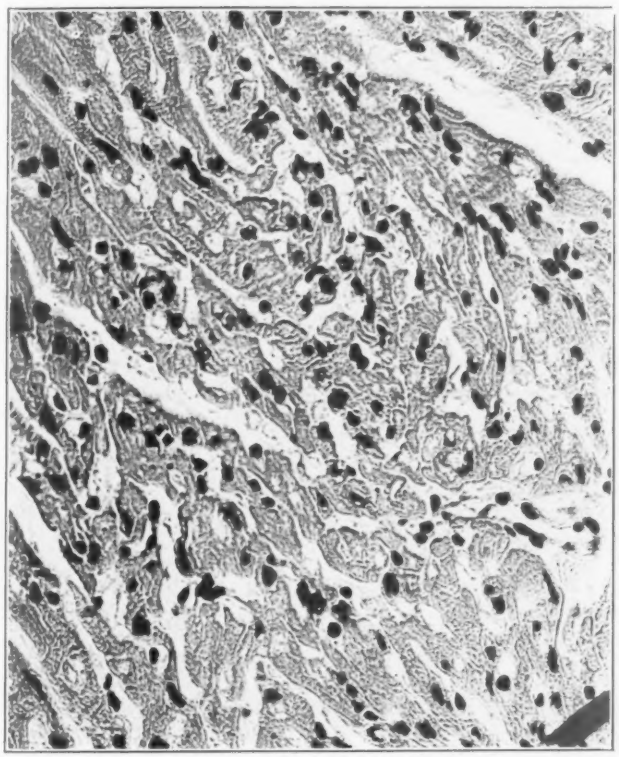

Fig. 5.—Medium power view of a section of heart muscle supplied by the thickened coronary branch. Note the edema of the muscle and loss of normal striations.

definite layer external to this and consisted of the usual number of longitudinal elastic fibers throughout which were the normal number of apparently unchanged longitudinal muscle cells. There was no cellular infiltration or cellular accumulations in the adventitia. Sections examined from the myocardium of both ventricles in the areas supplied by these coronary arteries showed a diffuse edema of the muscle cells with certain areas of hydrops and loss of striation (Fig. 5). The smaller branches of the coronary arteries within the myocardium were free from pathological changes. The diagnosis of congenital noninflammatory medial sclerosis of the coronary arteries was made.

For the purpose of comparative study the normal heart of a newborn infant was obtained at autopsy. The coronary arteries were not found to be prominent, opaque or cordlike, and the walls were thin and could readily be collapsed by the

slightest pressure. Microscopical sections were prepared from these normal arteries and stained with eosin-hematoxylin (Fig. 6) and picro-acid-fuchsin (Fig. 7) stains. The endothelium could readily be identified, and immediately external to this was the folded inner elastic membrane. The subendothelial tissue was lacking, thus making the tunica intima thin and distinct. In the tunica media the muscle cells were abundant, well stained, and formed a thick layer which was only sparsely invaded by elastic and connective tissue cells. The circular and radial elastic fibers were few in number and were not increased toward the tunica externa. The tunica externa consisted of longitudinally arranged connective tissue and elastic fibers, intermixed with an occasional muscle cell, and there was no definite formation of an external elastic membrane.

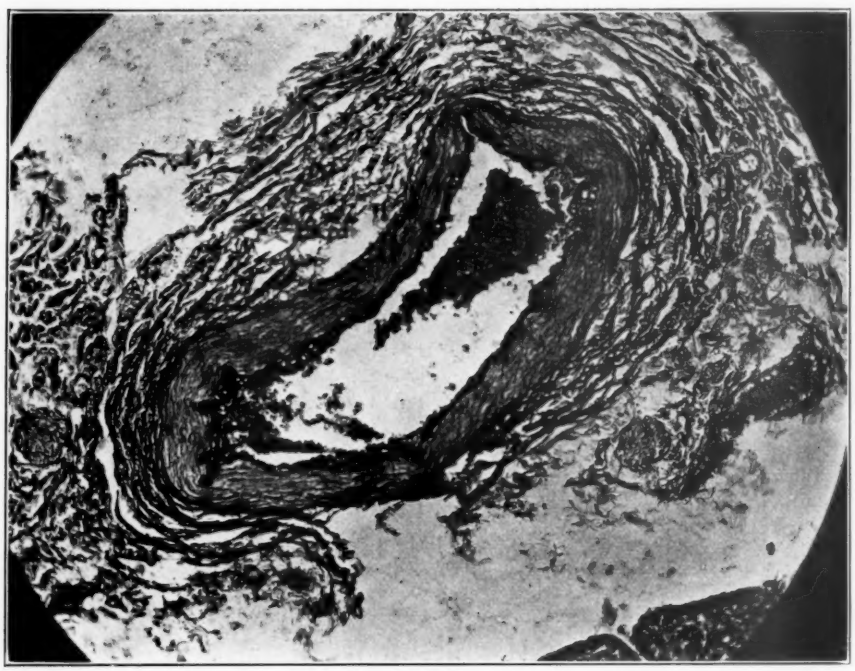

Fig. 6.—Eosin-hematoxylin stain of a normal coronary artery. Note the well-formed muscle cells in the media and the small amount of connective tissue.

PATHOLOGICAL DISCUSSION

This discussion is limited to those conditions in which the pathological changes involve the media primarily, disregarding atheromatosis and changes of the intima and adventitia which only involve the media secondarily.[54] The characteristics of these medial changes are connective tissue formations, calcification, fatty infiltrations and toxic and inflammatory degenerations, which are characterized by hyaline and amyloid replacements and which may be followed by calcified scars.

Degenerative changes varying from simple edematous infiltration to marked necrosis with complete disappearance of the elastic fibers have been frequently found following infectious-toxic diseases, such as scar-

let fever, diphtheria, measles, typhoid, influenza, pyemia, eclampsia and endocarditis.[12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24] These conditions lead to circulatory weakness which may be fatal, and are frequently found in the coronary arteries,[20, 21, 22, 23, 24] especially the anterior descending branch of the left coronary.[54] Depending upon the severity of the condition, the media may be restored to normal or may undergo scarring or calcification with the intima and adventitia remaining intact.[20] The cases of Hughes and Perry,[53] Durante,[51] Surbek[18] and Jaffé[19] appear to be of this type with resulting calcification.

These calcium deposits occurring in the medial layer, secondary to degenerative changes, are thought by Kaufmann[54] to be preceded by fatty

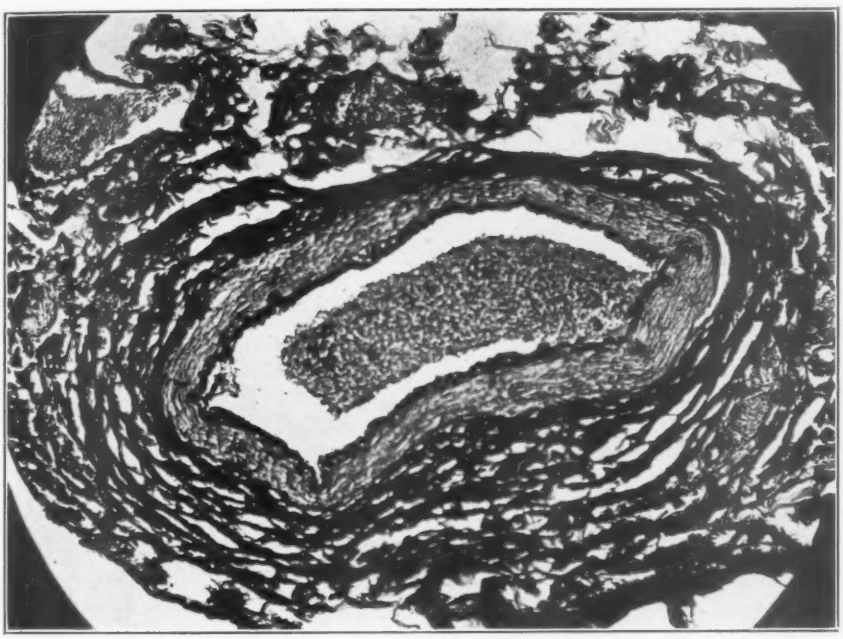

Fig. 7.—Picro-acid-fuchsin stain of a normal coronary. Note the normal thickness of the medial layer and few connective tissue cells.

and hyaline changes, while others consider them to be preceded only by the hyaline changes.[55, 56, 57] Wiedermann[58] believes that the process starts in the adventitial lymph sheaths and involves the media later. The mobilization and deposition of calcium in the media due to hypervitaminosis have been frequently observed,[43, 44, 45, 46, 47, 48, 49, 50] and, following irradiated ergosterol, necrosis of smooth and striated muscle in the rat is reported.[50] Kreitmar and Moll[49] believe that hypervitaminosis produces a mobilization of calcium, in which process calcific deposits develop in necrotic muscle foci, in healthy heart muscle and in otherwise unchanged elastic fiber, and they also demonstrate that the necrosis and calcification produced in arteries by vigantol is in reality true

medial calcification and is sharply differentiated from intimal sclerosis.

Calcification of the primary type always begins in the media between the muscle cells and consists of the laying down of calcium granules with the later replacement of the muscle fibers.[54] The muscle fibers are at first well preserved between the foci of calcium, and it is assumed that they degenerate secondarily.[10] This is true of the medial sclerosis of Mönckeberg in which there is usually no intimal change, although the intima may become stretched over wide calcified areas in the media, and has definitely been differentiated from arteriosclerosis by Mönckeberg[8, 9, 10] and by Fischer.[59] If we exclude hypervitaminosis with mobilization of calcium from the list of possible causes of this type of calcium deposition, we are led to the conclusion of Mallory[55] that the process is one of metaplasia of the fibroblastic elements. Orliansky[16] states that calcification of the medial layer of the coronary arteries is rare, while Mönckeberg[8, 9, 10] found it frequently, especially in the left coronary artery, beginning early in life.

The medial necrosis following infection[20, 21, 22 23, 24] and reported in the cases of Jaffé[19] and Gsell[60] is described as similar to the changes produced by Josué[34, 60] with the intravenous injection of adrenalin. The lesion is primarily localized in the media in its inner two-thirds and begins with fatty degeneration of the muscle cells and elastic fibers, and it is assumed that the fat arises from the broken down muscle cells and is followed by calcification.[61, 62, 63, 64, 65, 66] The intima and adventitia do not show changes. Dominguez[33] finds that spontaneous medial necrosis can also be produced in rabbits by uranium poisoning and that in such cases adrenalectomy did not prevent the development of the lesion.

Fatty degeneration in the media is common, occurring early in childhood and even in suckling infants.[54] The media of the smaller arteries of the brain, is especially prone to such change. This lesion is described as being the beginning pathological change in the sclerosis of Mönckeberg,[10] necrosis due to adrenalin,[62, 63, 64, 65] intoxication from alcohol and phosphorus, and the calcification from irradiated ergosterol.[68]

Connective tissue formation in the tunica media is usually inflammatory in origin, as in the case of McMicheal.[52] The case herein reported falls into this group but is unique in the entire absence of any infectious process, neither did it show fatty degeneration, necrosis, cell infiltration, or calcification. The case of congenital sclerosis reported by Hughes and Perry[53] is described as having a thickened intima and therefore is not considered primary medial sclerosis, while the case presented here showed the intima not to be involved. It is interesting to speculate as to whether this is not an early type of Mönckeberg medial sclerosis of the coronary arteries, in which the change is only one of hyaline and connective tissue, and in which further development of the process would result in calcium deposition within the tunica media.

The clinical findings of paroxysmal cyanosis and apnea with moderate cardiac enlargement and an electrocardiogram showing a slightly convex R-T interval followed by a sharp pointed negative T-wave in Lead I, suggest a possible method of diagnosing this condition before death. The T-wave in Lead I is very similar to the coronary T-wave described by Pardee.[69] This condition is present probably more frequently than a review of the literature would suggest, and all cases of the so-called congenital idiopathic cardiac hypertrophy should be investigated for these pathological findings.

CONCLUSIONS

1. A case of congenital medial sclerosis of the coronary arteries is reported with a review of the literature.

2. The process is noninflammatory and is characterized by a primary medial thickening, confined to the larger coronary branches.

3. The process is probably an earlier stage than those previously reported.

4. The electrocardiogram shows a T-wave similar to that seen in the more familiar types of coronary sclerosis.

5. The name of congenital medial sclerosis of the coronary arteries is suggested.

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RHEUMATIC HEART DISEASE:

I. Incidence and Rôle in the Causation of Death. A Study of 5,215 Consecutive Necropsies*

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THE incidence of heart disease may be determined by examining a large series of unselected post-mortem records and correlating this data with that concerning the clinical course of the illness. Such a combined morphological and clinical study is particularly essential to an accurate estimation of the incidence and importance of rheumatic heart disease, for statistics based on clinical studies alone may fail to include a considerable number of cases. Without a correlation of both clinical and morphological findings it would be difficult also to determine the degree of the cardiac damage caused by rheumatic fever. Furthermore it would be difficult to differentiate the various types of acute valvulitis, such as rheumatic, subacute bacterial, or malignant endocarditis. Thus, in the present study of the incidence of death from rheumatic heart disease it would have been impossible to classify approximately 30 per cent of the cases from the autopsy records alone.

It is conceivable that rheumatic fever may cause cardiac damage of such slight degree as to be unrecognizable on morphological examination. If cases of this type do occur they would obviously not be revealed by the present analysis.

METHOD OF INVESTIGATION

The material on which the present study was based consisted of 5,215 consecutive necropsy records from the Department of Pathology of the Boston City Hospital, covering a period from 1905 to 1929 inclusive, and compiled under the direction of Dr. Frank B. Mallory. These records represented gross and histological studies by various members of the staff. Each autopsy record had been reviewed by Doctor Mallory and the junior pathologists. Rheumatic and allied lesions were described without any attempt to classify or interpret their etiology. The term "vegetative endocarditis" appeared frequently in the final anatomical diagnosis; the term "rheumatic" was seldom used. The problem of etiology, therefore, was not influenced by the morphological diagnosis but was determined from the combined available data.

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No microorganism or immunological reaction has been found to be characteristic of rheumatic fever or of rheumatic heart disease; and as the clinical course and structural changes in the heart vary considerably, the diagnosis may present difficulties even when all available data have been studied. This is particularly true in the milder forms, which, as is true in other infectious diseases, may well occur more frequently than is suspected.

The few studies in the literature which report the incidence of rheumatic heart disease give no description of the method used in the selection of cases. It is possible that several important considerations were neglected in these studies. We had so much difficulty in distinguishing the rheumatic cases from cardiac diseases of other etiology, that a summary of the procedures followed in this selection seems essential.

The autopsy records were examined for such evidence of rheumatic heart disease as cardiac enlargement, acute or chronic pericarditis, myocarditis with Aschoff-like lesions on microscopical examination, acute valvulitis, chronic valvular sclerosis and associated sclerosis and shortening of the chordae tendineae and papillary muscles. Records showing sufficient evidence of rheumatic etiology were then correlated with the corresponding clinical data. The clinical aspects emphasized were: the age of the patient; a history of rheumatic manifestations, such as characteristic arthritis, chorea, and repeated attacks of severe tonsillitis and fever; the duration and character of the illness; and any clinical evidence of the existence of cardiac lesions or circulatory failure. The final selection was based upon a combination of these factors. Obviously such an analysis did not guarantee an absolutely accurate selection in each case. Rigid classification, however, in a disease of such wide variation would be unjustified.

THE PROBLEM OF DIFFERENTIAL DIAGNOSIS

A majority of the cases studied showed unmistakable evidence of rheumatic heart disease and were classified accordingly. It was difficult, however, to identify and evaluate that group in which the rheumatic heart disease, if present, was slight and the cardiac condition only a partial factor in causing death. It was necessary to differentiate these chronic stages of rheumatic endocarditis from atheromatous, luetic, and other types of sclerosis of the valves, and from endocarditis of other etiology. Examination of cases with uncomplicated primary atheromatous valvular heart disease revealed that the process involved only in rare instances cusps of the mitral as well as of the aortic valves, causing sclerosis and stenosis at the same time; and that senescent degeneration did not produce thickening and shortening of the chordae tendineae and papillary muscles similar to that in rheumatic heart disease. *Primary calcification of the valves* was uncommon; it occurred

generally in advanced age, and was usually associated with atheromatous lesions in the aorta. When the calcification involved the mitral valve, it was generally confined to the aortic mitral cusp and the gross character of this process, the usual fatty changes and frequently a calcified ring along the base of the mitral valve made it readily recognizable in most cases. The healed lesions in cases unmistakably of rheumatic etiology, on the other hand, occurred in practically every instance along the free margins, at the line of contact, causing thickening at the edges. These lesions contrasted strikingly with those of *syphilitic endocarditis* in which there is almost always widening of the commissures usually associated with luetic lesions in the aorta. Occasionally there was evidence that both etiological factors were present and such cases were listed accordingly.

In the course of the investigation several patients with acute vegetative lesions were examined; and it was again essential to determine which of these were truly rheumatic. Acute *bacterial endocarditis* secondary to a septic focus elsewhere in the body was recognized and excluded without difficulty: the presence of the primary infection, the friable irregular vegetations generally containing large numbers of bacteria, the suppurative processes and local evidence of destruction of the valves were sufficient to make the diagnosis definite. Effort was made to determine when such an acute vegetative process was superimposed on an old rheumatic process and such cases were listed separately. All cases showing a primary acute bacterial endocarditis were listed to determine the frequency of their occurrence in relation to old rheumatic lesions. The so-called *marantic* or *toxic acute endocardial* lesions occasionally seen in patients dying of tuberculosis, malignant tumors, and chronic nephritis were not a source of error. These lesions at most would have been included in the group of noncontributing rheumatic heart disease and in this group we noted only one case of acute rheumatic heart disease without the unmistakable old endocarditis accompanying it.

A few pathological descriptions mentioned delicate *adhesions between the valves of the aortic cusps.* Such adhesions were not regarded as indicative of a rheumatic process, for they occurred with fair frequency in patients with atheromatous involvement of the same valve. A rheumatic history was not obtained in these cases. In a few other instances hearts were observed with one or two *single vegetations* varying from one to five millimeters in diameter and occurring generally on the mitral or aortic and very rarely on the tricuspid or pulmonary valves. These cases also were excluded from the series for lack of other evidence as to their etiology.

In a number of cases details of the gross description of the acute vegetative process, post-mortem heart blood culture, and misroscopical examination of the valve, were lacking. Similarly the clinical

description occasionally did not contain the data needed to interpret the individual case. Three per cent of the cases taken under consideration were excluded because of such inadequacy. After a careful examination of the data in respect to the criteria indicated above, the cases with rheumatic heart lesions were classified into the groups listed in Table I.

TABLE I

DISTRIBUTION OF RHEUMATIC HEART DISEASE AMONG 5215 NECROPSIES

	NUMBER CASES
I. Rheumatic heart disease directly responsible for death	164
II. Rheumatic heart disease a contributing factor to death	41
III. Rheumatic heart disease associated with subacute bacterial endocarditis	35
Rheumatic heart disease with doubtful subacute bacterial endocarditis	6
IV. Rheumatic heart disease with superimposed primary malignant endocarditis	16
Rheumatic heart disease with subacute or malignant endocarditis	5
V. Rheumatic heart disease with secondary malignant endocarditis	2
VI. Rheumatic heart disease a noncontributing factor to death	205
Total	474

I. Rheumatic Heart Diseases Directly Responsible for Deaths.—This group includes patients in whom rheumatic heart disease or an immediate complication, such as mural thrombosis with embolism, was the cause of death. Patients in whom infections, such as pneumonia and erysipelas, occurred in the course of progressive and advanced heart failure were also regarded as rheumatic deaths.

The factors used in the classification of the cases in this group have been described above. A large percentage of the patients gave evidence of an active carditis with an acute vegetative process involving both mitral and aortic valves. These vegetations caused by rheumatic fever consisted of a series of closely aligned, pearly-gray, rounded bodies varying in diameter from 0.5 to 2.0 mm. and occurring regularly along the free margin of the valves. In the majority of instances the diameter was noted as 1 mm. or less. The aortic and mitral cusps, less commonly the tricuspid and rarely the pulmonary cusps were involved. At times the vegetations were described as slightly roughened and irregular in contour. They were generally adherent to the valve leaflet and could be detached only with great difficulty. In very acute lesions the vegetation was occasionally coated with fibrin, as indicated by microscopical examination, and when this accumulated, it occasionally resembled a friable vegetation, such as is seen in bacterial endocarditis. The rheumatic acute vegetations were free of bacteria except for a few instances in which there was question of bacterial complication. Ulceration in an old chronic rheumatic proc-

ess was extremely rare and when present suggested a healed process of an old malignant or subacute bacterial endocarditis.

Four of the patients listed in this group showed primarily a myocarditis with little or no evidence of an endocarditis. Idiopathic myocarditis might be considered but would be ruled out by the fact that in three of these patients there was a definite history of arthritis and fever, probably rheumatic; in one, a suggestive history recorded as "rheumatism."

II. Rheumatic Heart Disease a Contributing Factor to Death.—Patients dying of heart failure with pronounced rheumatic lesions were regarded as "rheumatic contributing" when the cardiac pathology was also the result of other etiological factors. The presence of arterial hypertension of long standing, coronary disease, or an associated severe anemia required this special grouping. In several of these patients death occurred beyond the age of sixty when such a factor as arteriosclerotic heart disease demanded consideration in the interpretation of the death.

III. Rheumatic and Subacute Bacterial Endocarditis.—In the entire series of 5,215 autopsies there were 47 cases of subacute bacterial endocarditis with and without evidence of an old rheumatic endocarditis. Of the 47 cases, 35 gave evidence of a previous rheumatic infection in the form of a definite old rheumatic endocarditis discovered by gross examination or from a characteristic clinical course. The records represent routine studies only, and although these were often elaborate and detailed in the presence of an atypical vegetative process, it is likely that the primary rheumatic basis in some of the remaining cases escaped detection. This is to be expected, for it is known that even slight valvular damage may serve as a basis for superimposed infection. Furthermore, the destruction occurring in subacute bacterial endocarditis is often sufficient to obscure underlying primary valvular damage. Again, in the group under consideration there was occasionally an unmistakable history of repeated attacks of rheumatic fever without evidence of a chronic rheumatic heart disease underlying the subacute bacterial process.

The vegetative process usually consisted of one or more conglomerated irregular masses varying from 2 mm. to 1 cm. in diameter, and distributed over the mitral, aortic, and, rarely, the tricuspid valves. The left auricular endocardium was frequently involved in a widespread process which extended over the mitral cusps, chordae tendineae, and papillary muscles, causing ulceration and destruction. These masses of vegetations were regularly friable, and microscopical examination generally revealed large numbers of streptococci. In the early stage the vegetations were often small and at times discrete. The irregular friable character, the positive microscopical findings, and the clinical observations made the diagnosis definite in most cases.

In contrast to the rheumatic group with an active carditis, secondary anemia was regularly present in cases with subacute bacterial endocarditis. The frequent occurrence of embolic phenomena secondary to mural thrombi and possibly fibrinous rheumatic vegetations in cases of rheumatic heart disease interfered with the application of "embolic phenomena" as differential criterion between subacute bacterial and rheumatic endocarditis.

Bacterial processes showing Streptococcus viridans either in antemortem blood culture or early post-mortem vegetation culture, or histological sections were generally classified in this group. In a few cases it appeared that a Streptococcus viridans infection with a subacute bacterial course gave evidence of terminal infections with a pneumococcus or staphylococcus. Cases of this kind were classified in the subacute bacterial group. Vegetations yielding Staphylococcus aureus as the predominant organism were classified in the group of malignant endocarditis. The latter group, although not sharply defined, presented a more acute clinical picture with a shorter duration of the illness, a more fulminating termination, a greater tendency to local destruction and perforation of the valves and to septic emboli.

In one group of cases it was difficult to decide whether an acute process associated with an old rheumatic endocarditis belonged to the rheumatic manifestations or represented a secondary bacterial endocarditis, possibly of Streptococcus viridans origin. In 6 cases no decision could be reached because of insufficient data or the atypical character of the lesions. In all 6 cases, however, there was undoubted evidence, clinical and morphological, of an old rheumatic process.

IV. Rheumatic Heart Disease With Primary Malignant Endocarditis.—Cases in this group were often not clearly distinguishable from those in Group III. In general, patients showing an acute or subacute bacterial infection that developed on the basis of old valvular damage and was caused by Staphylococcus aureus, Streptococcus hemolyticus, pneumococcus, gonococcus or meningococcus, and not by Streptococcus viridans, were classified in this group. Other sources of the bacteremia than the vegetations were not found in these cases. Further indications in the classification were the more fulminating acute illness of septic character, and the tendency to marked local destruction and the formation of septic emboli as noted above. Although ulceration and destruction of the valve occasionally occurred in subacute bacterial endocarditis of Streptococcus viridans origin, it was almost a constant finding in the malignant group. Undoubtedly, some cases listed in this group might more properly have been listed in Group III and *vice versa*.

Although an effort was made to find cases of this type which occurred primarily on a normal valve, none was evident. In all 14 cases

of the group unmistakable evidence of either a previous rheumatic endocarditis or a clinical history of early rheumatic fever was present.

V. Rheumatic Heart Disease With Secondary Malignant Endocarditis.—Two patients with a primary septic focus in the lungs and kidneys respectively showed an old rheumatic lesion associated with a superimposed acute bacterial endocarditis. In a picture of this complexity it was difficult to determine to what extent the cardiac lesions contributed to death. The patient might have died from the pneumonic process or the pyelonephrosis regardless of the endocarditis, or possibly from a primary acute malignant endocarditis, the distal process being really secondary to it. The pathogenesis not being clear from the history and clinical findings, these cases were listed as a secondary invasion of the valves, from the focus elsewhere in the body.

VI. Noncontributing Rheumatic Heart Disease.—In this group were listed those cases in which death was not due to the rheumatic pathology. The criteria by which the mild rheumatic process was detected were often not absolutely definite. In the 205 cases listed in this group the valvular process was graded as moderate or marked in 100. These cases were definitely rheumatic. The remaining 105 showed slight but definite mitral and aortic endocarditis. In all cases the process was located along the free margin of the valves. Slight thickening of the free margins of the valves is a common post-mortem finding, particularly after the fifth decade of life, and may be an expression of senescent sclerosis. The thickening regarded here as probably of rheumatic origin should not be confused with this for the following reasons: the sclerotic changes are much more common than the mere 5 per cent of the cases noted; the age variation in this group with slight involvement indicated a wide distribution with numerous cases below the age of forty; and the examiners did not list all cases with thickening of the free margins as cases of endocarditis, but did record and list as "endocarditis" over 95 per cent of the 105 cases considered here as probably rheumatic. Furthermore, the cases were evenly distributed over the entire twenty-five year period of analysis, suggesting that the examiners recognized these cases as different from those of the usual valvular thickening. Finally, the distribution to both mitral and aortic cusps paralleled that of the cases with advanced rheumatic endocarditis. The occurrence of mild grades of any disease is to be expected and for the above reasons it appears that these cases probably represent valvular pathology due to a mild rheumatic infection and something more than the diffuse increase in thickness of the free valvular margins seen so commonly in routine post-mortem examinations.

DISCUSSION

Exact information concerning the incidence and relative significance of the various types of heart disease is important, particularly from

the point of view of public health. The efficacy of preventive and therapeutic measures commonly used in heart disease can be evaluated only by a study of reliable statistical data. Such information, moreover, may throw light on such etiological factors as race, geographic location, and climate.

Numerous statistical sources may give significant information regarding the incidence of heart disease, but at present the value of available reports is impaired by the unreliability of the original data. Statistics on the morbidity rate, for example, are based on clinical evidence alone and are therefore as subject to inaccuracy as the diagnosis on which they are based. The figures on mortality rate derived from death certificates are notoriously unreliable. The statistics, even of hospitals, are often of doubtful value because of confusion in the classifications of diseases and insufficient effort in differentiating between primary and contributory causes of death.

Practically no information is available concerning the incidence of rheumatic heart disease. The criteria of diagnosis and the methods of accumulating data on this subject vary widely. Cohn,[1] after reviewing the literature regarding factors which influence rheumatic heart disease, concludes: "The data inspire no great confidence and suggest that the conditions under which they are correlated should be more precisely defined."

Harrison and Levine[2] report the occurrence of mitral stenosis 64 times in 1,362 consecutive necropsies at the Peter Bent Brigham Hospital, an incidence of 4.69 per cent. Of 15,932 medical admissions to this same institution between the years 1914 and 1923, 3.89 per cent gave clinical evidence of mitral stenosis. These data obviously cannot be regarded as an indication of the incidence of rheumatic heart disease and occasionally such stenosis is due to atheromatous sclerosis. This is illustrated by our finding of only 66 cases of mitral stenosis among the total 164 cases with marked rheumatic heart disease. If we had judged the frequency of rheumatic heart disease by the cases of mitral stenosis alone, we would have obtained a frequency of only 4.0 per cent, comparable to the figure of Harrison and Levine, instead of 9.1 per cent. Cabot[3] analyzed 4,000 necropsy findings in the Massachusetts General Hospital for the period from 1896 to 1919. He reported 208 cases of "rheumatic valvular heart disease" but apparently did not classify all the types of cardiac damage produced by rheumatic fever.

Of the 5,215 necropsy records in the present investigation, 486 cases of cardiac pathology were classified as of rheumatic origin, an incidence of 9.3 per cent. If we subtract from the rheumatic series the cases with subacute endocarditis in which evidence of rheumatic etiology could not be established, the incidence is 9.1 per cent. If the 105 cases with slight cardiac lesions are not included in the total group

of rheumatic heart disease, the incidence of the remaining cases is 7.1 per cent. This incidence of 9.3 or 7.1 per cent respectively is distinctly higher than had been expected from the few available reports in the literature. There may be a number of explanations for this difference. The high incidence, in the first place, is reported from a locality where rheumatic fever is probably conspicuously prevalent.[2, 4] Furthermore, these observations are from a municipal hospital which cares mainly for patients of limited means, drawn for the most part from the crowded sections of a large city. Insufficient nutrition and light, the influence of which on rheumatic heart disease is important may partially account for the relatively frequent occurrence of the condition in the present series. The most important factor in the explanation of the high incidence noted, however, is that in previous reports only the obvious and marked lesions were recognized. In the present study, on the other hand, equal attention was given to the less pronounced but nevertheless distinct endocardial and myocardial lesions. These milder cardiac lesions, probably, were the outcome either of a mild rheumatic fever or of a more severe attack from which recovery was more complete. These mild lesions, as a rule, produced few or no clinical signs. The frequent occurrence of slight rheumatic cardiac lesions may be compared with the common "forme fruste" manifestations of other infectious diseases, such as pulmonary tuberculosis. Leary reports the occurrence of rheumatic endocarditis without systemic manifestations as a frequent accidental finding in a number of medico-legal autopsies.[5] This observation also shows that rheumatic heart disease not infrequently runs a symptomless course. The occurrence of mitral stenosis in approximately 4 or 5 per cent of the total number of admissions to the larger Boston hospitals[2] is, then, in proportion to the 9.3 per cent frequency of rheumatic cardiac damage reported here, for obviously the latter figure, which includes cases without clinical signs, must be considerably higher. Furthermore, Pribram[6] states that from 2 to 5.5 per cent of all admissions to the German and Scandinavian hospitals are rheumatic cases, and in England the frequency of rheumatic fever reaches as high a level as 7 to 11.5 per cent of all admissions. The high incidence of rheumatic heart disease reported here would make rheumatic fever a rather prevalent disease comparable to carcinoma; as the frequency of carcinoma among 3,004 autopsies in the Boston City Hospital between 1910 and 1928 inclusive, was 10.4 per cent.[7]

Rheumatic heart disease occurred in 56.6 per cent of the males in the total group with rheumatic heart disease; in 43.4 per cent of the females in that group. This indicates a moderately increased incidence of rheumatic heart disease in the female sex, since the sex ratio in 5,060 autopsies during the same period of years was 62 per cent

TABLE II

DISTRIBUTION OF RHEUMATIC HEART DISEASE ACCORDING TO SEX AND COLOR

	MALE	FEMALE	COLORED
I. Rheumatic heart disease directly responsible for death	82	82	10
II. Rheumatic heart disease a contributing factor to death	26	15	1
III. Rheumatic heart disease associated with subacute bacterial endocarditis	33	13	4
Rheumatic heart disease with doubtful subacute bacterial endocarditis	5	1	0
IV. Rheumatic heart disease with superimposed primary malignant endocarditis	13	3	2
Rheumatic heart disease with subacute or malignant endocarditis	1	4	0
V. Rheumatic heart disease with secondary malignant endocarditis	110	95	1
VI. Rheumatic heart disease a noncontributing factor to death	2	0	0

male to 38 per cent female. This finding accords with the clinical impression that the disease occurs somewhat more frequently in females.

Eighteen, or 3.8 per cent, of the 474 patients with rheumatic heart disease were negroes; but since 8 per cent of the 5,060 consecutive autopsied cases were in negroes, the actual incidence of rheumatic heart disease in this racial group is relatively lower. Whether this difference is inherent in the race, or is due to migration after childhood from a warmer climate where rheumatic fever is a rare disease[2, 4] cannot be stated. Clinical impression suggests that native negroes and northern whites are equally susceptible to rheumatic fever. The lower incidence would thus appear to be due to migration. The finding of rheumatic heart disease in 3.8 per cent of the post-mortem examinations of negroes probably, therefore, represents an average of these two different sections of the negro population.

SUMMARY AND CONCLUSIONS

1. Among the 5,215 consecutive necropsy examinations of patients from the poorer class who were cared for in the Boston City Hospital between the years 1905 and 1929 inclusive, a combined clinical and morphological study revealed rheumatic heart disease in 474, or 9.1 per cent, of the cases.

2. Rheumatic heart disease was found in 56.6 per cent of the males, and in 43.4 per cent of the females in the group with rheumatic heart disease. The sex distribution in the total necropsy examinations was: males, 62 per cent; females, 38 per cent. Thus rheumatic heart disease was slightly more prevalent among the females.

3. Eighteen, or 3.8 per cent, of the total number with rheumatic heart disease were negroes. Eight per cent of the autopsied patients were negroes. This would indicate that rheumatic heart disease oc-

curs only about half as frequently among negroes living in New England as among the white race.

4. Rheumatic heart disease was directly responsible for death in 164 instances, or 34.5 per cent of the total group with rheumatic heart disease.

In an additional group of 41 cases, corresponding to 8.6 per cent of all the cases in this group, subacute bacterial endocarditis was superimposed on rheumatic heart disease. In 21 cases, corresponding to 4.4 per cent of these cases, malignant endocarditis developed in association with rheumatic heart disease. In 2 additional cases, secondary malignant endocarditis was independent of the rheumatic heart disease. As the subacute and primary acute endocarditis developed on previously damaged rheumatic valves, in this group, representing 13 per cent of all cases with rheumatic heart disease, death was caused indirectly by rheumatic heart disease.

Rheumatic heart disease contributed to death in 41 instances, or 8.6 per cent, of the total cases.

In 205 cases, or 43.2 per cent of the cases with rheumatic heart disease, the character of the cardiac involvement was such that the lesions did not contribute to death.

5. Rheumatic heart disease is surprisingly prevalent among the poorer section of the population of Boston. Its frequency (9.1 per cent) approaches that of carcinoma (10.4 per cent).

6. Rheumatic heart disease frequently exists as a mild "forme fruste" manifestation, without causing obvious impairment of the circulation.

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STUDIES IN CONGESTIVE HEART FAILURE

XVI. The Clinical Value of the Ventilation Test in the Estimation of Cardiac Function*

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IN THE tenth paper[1] of this series a method of estimating cardiac function was described. This depended on the fact that upon the performance of exercise the degree of dyspnea produced is directly proportional to the ventilation and inversely proportional to the vital capacity. It was shown that variations in the nutritional state of the subjects had a marked effect on the results obtained and hence in order to compare obese persons with thin ones a correction factor for body weight was introduced. The value so arrived at was called the "ventilation index." In this study are reported the results of applying this test to 21 normal persons and to 79 patients.

The test as originally described consisted of performing exercises of four different degrees. As the severest of these (Exercise IV of the former paper) is rather too strenuous for most patients, it has been omitted in this study. Furthermore, whenever a subject had severe dyspnea on the performance of any degree of exercise, the exercises of severer degrees were omitted.

The patients had a careful history and physical examination. Teleroentgenograms and electrocardiograms were made in the majority of cases, and in a number of instances blood studies were made and basal metabolic rates were determined. Since it was shown in the previous study[1] that patients with hyperthyroidism, with severe anemia, and with chronic pulmonary fibrosis from any cause, usually had high values (i.e., values similar to those found in persons with cardiac disease) on performance of the test, all persons with these disorders were excluded from the present series.

The subjects were classified into groups as follows:

I. Normal: i.e., no symptoms referable to the heart and no evidence of cardiac disease: 21 cases.

II. Cardiac Neurosis: 16 cases.

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III. Organic Cardiac Disease:

A. Asymptomatic: 10 cases:
B. Symptoms on exertion only: 21 cases.
C. Mild symptoms at rest: 16 cases.
D. Severe symptoms at rest: 16 cases.

The classification was based entirely on the data other than those obtained from the ventilation test.

The majority of the patients were followed clinically for periods of a year or more after the ventilation test had been made. The clinical data were then compared with those obtained from the ventilation studies and by this means an attempt has been made to evaluate the clinical significance of the method.

The limits of the normal are not sharp for any laboratory test. It was shown in a previous paper[1] that the ventilation index varied within rather wide limits in normal subjects. It was found, however, that the majority of normal subjects had ventilation indices below the levels of 20, 25, and 30 for the three exercises, respectively, and that no normal subject had a curve above each of these points. For this reason we have, in the present paper, classified the values as follows:

1. "Normal" curves; when all points were below the 20-25-30 curve.
2. "High" curves; when all points were above this curve, and
3. "Doubtful" curves when one or more points were above and one or more points were below the 20-25-30 curve.

RESULTS

A summary of the data is shown in Table I. The findings may be conveniently considered from several different points of view.

A. *The Value of the Ventilation Test in Diagnosis; i.e., in Determining Whether a Patient Has or Has Not Organic Heart Disease.*—As can be seen from Table II, 2 of the 21 normal subjects in the present series had "doubtful" curves; the remaining 19 persons having "normal" values. Of the 16 patients with cardiac neurosis, none had "high" curves, 4 had "doubtful," i.e., borderline curves, and 12 had normal curves. Seven of 10 patients with asymptomatic organic cardiac disease had "normal" curves, 2 were "high" and 1 was "doubtful." Of 21 patients who had organic cardiac disease and symptoms only on exertion, the ventilation test was "normal" in 2; "doubtful" in 4 and "high" in 15. One patient with symptoms at rest had a "doubtful" curve; the other 31 such subjects were "high." No person with symptoms at rest had a "normal" curve.

From these data it seems clear that the ventilation test is of little or no value as a purely diagnostic measure. It is true that as a general rule patients with normal hearts and with cardiac neurosis have normal values, but so do patients with asymptomatic organic cardiac

TABLE I

VALUES FOR THE VENTILATION INDEX IN NORMAL SUBJECTS, PATIENTS WITH CARDIAC NEUROSIS, AND PERSONS WITH ORGANIC CARDIAC DISEASE IN VARIOUS STAGES

GROUP	NUMBER OF SUBJECTS	VITAL CAPACITY PER SQ. METER, LITERS			VERY MILD EXERCISE						MILD EXERCISE						MODERATE EXERCISE					
					VENTILATION PER SQ. METER, LITERS			VENTILATION INDEX			VENTILATION PER SQ. METER, LITERS			VENTILATION INDEX			VENTILATION PER SQ. METER, LITERS			VENTILATION INDEX		
		LOWEST	HIGHEST	MEAN	LOWEST	HIGHEST	MEAN	LOWEST	HIGHEST	MEAN	LOWEST	HIGHEST	MEAN	LOWEST	HIGHEST	MEAN	LOWEST	HIGHEST	MEAN	LOWEST	HIGHEST	MEAN
Normal	21	1.73	2.84	*2.19*	26.9	43.5	*36.4*	11.5	21.9	*16.9*	34.5	50.5	*43.3*	13.7	24.5	*20.2*	41.4	59.5	*51.5*	15.7	30.1	*23.7*
Cardiac neurosis	16	1.43	2.88	*1.96*	26.4	43.2	*35.2*	14.8	22.6	*17.8*	33.5	55.4	*45.1*	18.2	25.3	*22.2*	38.8	62.7	*49.3*	19.6	32.7	*25.0*
Asymptomatic cardiac disease	10	1.46	3.28	*2.23*	32.8	43.3	*38.0*	15.1	23.4	*18.5*	41.4	54.9	*47.1*	16.8	28.8	*22.2*	45.4	64.4	*54.0*	19.7	31.3	*25.3*
Cardiac disease Symptoms on exertion only	21	1.09	2.34	*1.69*	25.3	64.7	*41.2*	13.9	34.8	*23.8*	36.4	74.0	*54.5*	19.6	42.0	*31.4*	41.3	88.1	*59.7*	21.5	49.9	*35.4*
Cardiac disease Mild symptoms at rest	16	0.91	2.12	*1.63*	31.6	64.6	*47.5*	18.9	37.9	*32.2*	48.1	79.5	*60.9*	27.7	48.3	*38.8*	----	----	----	----	----	----
Cardiac disease Severe symptoms at rest	16	0.86	1.94	*1.33*	44.6	85.2	*58.9*	23.7	63.0	*44.0*	----	----	----	----	----	----	----	----	----	----	----	----

disease. Furthermore, one may occasionally encounter a "doubtful" or borderline test in a patient with advanced cardiac disease, as well as in normal subjects and in persons with cardiac neurosis. In about 80 per cent of the cases one can make the correct diagnosis as to the presence or absence of organic heart disease from the ventilation test alone, but this use of the test becomes unimportant when one remembers that by history and physical examination alone a correct opinion can be arrived at in about 90 per cent.

TABLE II

A SUMMARY OF THE VALUES FOR VENTILATION INDEX IN RELATION TO THE CLINICAL STATE

GROUP		NORMAL	DOUBTFUL	HIGH
		NUMBER OF CASES	NUMBER OF CASES	NUMBER OF CASES
	Normal subjects	19	2	0
	Patients with cardiac neurosis	12	4	0
Patients with organic cardiac disease	Asymptomatic	7	1	2
	Symptoms on exertion only	2	4	15
	Mild symptoms at rest	0	1	15
	Severe symptoms at rest	0	0	16

B. *The Value of the Ventilation Test in Prognosis.*—It was shown in the previous paper that in a given patient progression or retrogression of congestive failure could be followed accurately and expressed quantitatively by means of the ventilation test. Changes in the ventilation index are therefore of value in prognosis. The next question

TABLE III

THE VENTILATION INDEX IN RELATION TO PROGNOSIS IN PATIENTS WITH CARDIAC DISEASE

CHANGE IN CLINICAL STATE IN 12 TO 18 MONTHS	PATIENTS WITH NORMAL VALUES (20 OR LESS)*	PATIENTS WITH MODERATE INCREASE (20 TO 40)*	PATIENTS WITH MARKED INCREASE (40 OR MORE)*
No progression: Cardiac symptoms unchanged or improved	9	16	4
Progression: Cardiac symptoms more severe	0	6	2
Dead	0	2	7
Total cases	9	24	13

*The patients are tabulated according to their ventilation indices for the mildest exercise. They have been followed for from twelve to eighteen months since the observations concerning the ventilation index were made.

is: Can one make a fairly accurate prognosis in regard to a given patient from the results of a single test? Data bearing on this point are shown in Table III, in which the follow-up records for 46 of the subjects are summarized. (All persons were followed for at least a year and some for more than a year after the test.) It can be seen that, in general, the deaths occurred in the subjects who had high values for the ventilation index, and that those with the lowest values usually remained relatively free of symptoms of congestive failure.

However, in the intermediate group, i.e., those with only moderately increased ventilation indices, 2 patients died, 6 were worse, and 16 improved. Even in the group with very high values, 4 patients are better now than they were a year ago.

C. *The Value of the Ventilation Test in Neurotic Patients With Organic Cardiac Disease.*—The facts previously mentioned seemed to indicate that the ventilation test does not supply, in the majority of patients, helpful information in addition to that which can be acquired by the more usual methods. However, in a certain group of cases it seemed to us to yield knowledge which is of aid both in prognosis and in treatment. We refer to those patients who in addition to having definite clinical evidence of organic cardiac disease are also nervous, hypersensitive, and have symptoms of functional origin referable to the heart. This combination of organic heart disease plus cardiac neurosis may occur in men but is seen most frequently in young females with rheumatic heart disease and in women with hypertension and various functional vascular disturbances associated with the menopause. In such a case one may make the most exhaustive clinical, electrocardiographic, and roentgenologic studies and still be in doubt as to how much of the patient's dyspnea is dependent on the organic disorder and how much is related to the oversensitive psyche. The decision is an important one because not only prognosis but treatment depends upon it.

It is in this type of patient that we believe the ventilation test gives information which cannot be obtained by any other means. In the series of 100 subjects who performed the test in the present study there were 12 such cases. By way of illustration brief abstracts of 5 of these cases are presented.

CASE REPORTS

A medical student had had rheumatic fever twice in childhood. During his third year in medical school he began to notice occasional palpitation and some dyspnea on climbing stairs. He was not highly neurotic but was somewhat apprehensive. Examination revealed a cardiac impulse just outside the midclavicular line. There were characteristic signs of mitral stenosis and of aortic insufficiency. The heart rate was 90; the rhythm regular. Lungs, liver, and extremities were normal.

Clinical Diagnosis: Chronic rheumatic endocarditis of aortic and mitral valves. Questionable mild cardiac neurosis.

Teleroentgenogram revealed slight cardiac enlargement; electrocardiograms were normal except for left axis deviation.

The values for the ventilation index were 15.1, 16.8 and 19.7 (upper normal limits 20-25-30) for the three exercises, respectively. He was reassured and told that his dyspnea was probably due to apprehension rather than to his cardiac disease. He has had no further symptoms although he leads a normal, active life.

Mrs. H. McC., aged fifty-seven years, complained of indigestion, belching, intermittent diarrhea with mucous stools, nervousness, "quivering spells," and insomnia. She suffered palpitation and dyspnea on stair climbing when nervous and when she had abdominal distention. The cardiac rate was 90; the rhythm regular. The impulse was felt 1.0 cm. outside the midclavicular line. All the cardiac sounds were somewhat accentuated. There were no murmurs. The peripheral vessels were soft. The blood pressure was 158/98 mm. The arteries were not abnormal. There was no evidence of visceral congestion and no edema. Electrocardiogram was normal. Teleroentgenogram showed a cardiac shadow at the upper limits of normal size.

Clinical Diagnosis: Psychoneurosis, hypertension, slight cardiac enlargement.

Despite the slight cardiac enlargement it was our impression that her cardiac symptoms were mainly due to the functional state. However, the values for the ventilation index for the three exercises were 23.0, 35.6 and 45.3 (upper normal limits 20-25-30). In view of this she was given digitalis with rapid and rather striking improvement. Several months later she omitted digitalis and, following an attack of influenza, she developed frank congestive failure.

Mr. J. B. B., aged fifty-one years, had chronic cholecystitis. He was a high-strung, introspective person, given to crying spells and had had a "nervous breakdown" several years previously. He was decidedly "heart-conscious" and often had palpitation on lying down. He had never noted dyspnea. He had had rheumatic fever when twenty-five years old. The heart was not enlarged. The rate was 90; there was an occasional premature beat. At the apex a very high-pitched musical systolic murmur was heard. This was louder with the patient sitting than when he was recumbent and the intensity was greater after exercise than at rest. There were no signs of pulmonary or systemic congestion. Peripheral vessels were soft. Blood pressure was 122/80 mm. Electrocardiogram was normal; teleroentgenogram revealed a normal sized cardiac shadow.

Clinical Diagnosis: Chronic cholecystitis, cardiac neurosis, mild chronic rheumatic endocarditis of mitral valve—not progressive.

The curve for the ventilation test was lower than the average for normal persons. He was reassured and given no other cardiac therapy. He has continued to have occasional palpitation but no longer fears it. He still is dyspnea-free.

Mrs. W. N. B., aged forty-eight years, complained of "hot flashes," "cold chills," nervousness, and dyspnea. She had not menstruated for six months. Since an attack of influenza thirteen years previously she had noted dyspnea on rapid walking. In the past few months she had had "choking and smothering spells" when nervous and believed that she was more dyspneic on exertion than previously. She was never dyspneic at rest except when nervous. She was considerably overweight. The maximum point of cardiac impulse was 2 cm. outside the midclavicular line. The cardiac borders were indistinct by percussion. The rate was 90; the rhythm regular. There were no murmurs. The cardiac sounds approached each other in quality. The arteries were not thickened. Blood pressure was 160/104 mm. The lungs were clear, the liver was not felt; there was

no edema. By x-ray examination the heart appeared to be just at the upper normal limit in size. The electrocardiogram revealed left axis deviation.

Clinical Diagnosis: Obesity, hypertension, probable cardiac enlargement, menopause, cardiac neurosis.

Values for the ventilation test were 25.3, 30.1, and 39.2 for the three exercises as compared to 20-25-30, the upper normal limits. Following digitalis and reduction of her weight, her dyspnea improved considerably.

Mrs. A. J. C., aged twenty-six years, desired to know whether it was safe for her to have a baby. When she was fourteen years old, she was told she had a heart murmur, and was instructed to limit her exercise to slow walking. She had never had any symptoms referable to the heart other than dyspnea on walking rapidly uphill. She was not neurotic. The heart was not enlarged either by physical examination or by x-ray. There was a very loud, rough systolic murmur at the pulmonic area. The pulmonic second sound was rather faint. Electrocardiogram showed right axis deviation. Fluoroscopy revealed prominence in the region of the pulmonic artery. The heart was apparently not enlarged.

Clinical Diagnosis: Congenital cardiac disease, either patent ductus arteriosus or pulmonic stenosis of slight degree.

The values for the ventilation index were just at the upper normal limits. She was told to have the baby if she so desired. When last heard from she had passed through a normal pregnancy and a normal labor and had had no symptoms referable to the heart.

It was our belief that in each of these cases the data obtained from the ventilation test were of some value in prognosis and treatment. As has been stated, we do not believe the method is of any great value, except as a means of research in other types of cases.

SUMMARY AND DISCUSSION

1. Measurements of the vital capacity and of the ventilation upon the performance of a series of standardized exercises were made on 100 subjects. Of these, 21 were normal, 16 had cardiac neurosis, 10 had organic cardiac disease without symptoms, 21 had dyspnea on exertion only, and 32 had, in addition to dyspnea on exertion, some respiratory discomfort at rest. From the measurements a value called the ventilation index, which is a fairly close objective expression of the degree of dyspnea, was calculated.

2. Analysis of the data shows that the determination of the ventilation index is of little or no value in the diagnosis of the presence or absence of organic heart disease, because patients with cardiac neurosis, patients with asymptomatic cardiac disease and normal subjects all occasionally have borderline tests, although the majority of patients in these groups have normal values. Patients with cardiac dyspnea nearly always have high values for the ventilation index but in such patients the customary methods of study are usually adequate to establish a diagnosis of the presence of organic cardiac disease.

3. In a given case repeated determinations of the ventilation index may be of considerable value in prognosis. Single tests give relatively

little information as to the outlook. In general, the patients with low values have a good prognosis and those with very high values have a poor outlook but exceptions are fairly numerous because the test only measures the degree of dyspnea at the moment, and is not influenced by such extremely important factors as the liability to infection, the tendency to thrombosis or the likelihood of coronary and other vascular accidents.

4. The ventilation test appears to be of definite clinical value in one group of cases: namely, in those patients who have both organic and functional disorders referable to the heart. Such instances are not uncommon and the ventilation test allows one to determine with fair accuracy how much of the patient's dyspnea is due to the cardiac neurosis and how much to the cardiac disease. This information, which cannot be obtained by any other method may be of considerable value in prognosis and in treatment.

5. The chief value of the ventilation test is in research, because it provides a method for determining quantitatively the effect of various therapeutic measures on dyspnea.

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DEPRESSION OF THE VOMITING REFLEX BY THE DIGITALIS BODIES*

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THE emetic action of the digitalis bodies has been the subject of numerous experimental investigations. These have dealt mainly with its mechanism and the conditions under which these drugs induce vomiting.[1] It is a very familiar phenomenon in both animals and man that a moderately toxic dose induces one or two attacks of vomiting and as the dose is increased vomiting continues and becomes more intense. There may be remissions lasting several hours; then the vomiting recurs and may continue for a day or two after the drug has been discontinued. The drug sometimes causes death in dogs and cats without having produced vomiting. After a very large intravenous injection a convulsion and death may occur within a few seconds; this does not appear to allow sufficient time for vomiting to take place. We have, however, seen cats die even after an intramuscular injection of ouabain without vomiting. Under ordinary conditions such observations are rare.

Several years ago in the course of a study of digitalis elimination, one of us[2] observed what appeared to be an interference with the vomiting mechanism after repeated injections of digitalis. It was noted that after small doses were injected daily intravenously in several cats there came a point when sufficient cumulation had taken place to induce vomiting. The next few daily doses continued to cause vomiting, but the last two or three daily doses before the animal died no longer produced emesis. In those experiments electrocardiograms were not taken. Such a change in the response of the vomiting reflex to the digitalis bodies might be of considerable practical importance in view of the fact that reliance is generally placed on nausea and vomiting as signs for discontinuing digitalis in order to avoid serious overdosage.

The present study was undertaken to extend these observations and to determine whether it be possible, by the repeated injections of the digitalis bodies, to diminish or abolish the emetic action of the drugs while at the same time increasing the intensity of the cardiac poisoning.

EXPERIMENTAL

Preliminary experiments were performed on cats. Fifteen animals were given repeated intravenous injections of digitoxin, ouabain, or the tincture of digitalis until death, and the occurrence of nausea and

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vomiting after each dose was noted. No electrocardiograms were taken because cats are too excitable to permit the taking of satisfactory tracings unless they are restrained or anesthetized, and both of these procedures interfere with vomiting.

The essential results are based on a series of experiments carried out on six dogs. The digitalis bodies, digitoxin, ouabain, and the tincture of digitalis, were always injected intravenously. The size of the individual doses and the intervals were varied for every experiment. It was planned to have the individual doses* so small as to make it possible to detect the order in which different changes might appear. On the other hand, inasmuch as the animal would usually refuse food during the experiment, it was desirable to give doses large enough so as not to prolong the experiment beyond a few days, since prolonged starvation might introduce complicating factors.

Electrocardiograms were taken at intervals before and after the injection of the drugs. Tracings were obtained at such times as to record the immediate, as well as the delayed, effects. Only Lead II was taken. The animal was allowed to sit or lie quietly on the table without anesthesia or restraint. In all more than 200 electrocardiograms were examined. The interpretation of some of the changes presented considerable difficulties, some being due to shifting of the electrical axis of the heart when the animal stood up to vomit. The T-wave, in particular, was extremely variable (Fig. 3). The only changes in the electrocardiogram that were attributed directly to the action of digitalis were extreme slowing of the sinus rate, marked depression of the R-T segment, ventricular ectopic beats, ventricular tachycardia, and A-V block.

Nausea and vomiting were regarded as signs of stimulation of the vomiting reflex. Retching was considered tantamount to vomiting, and whether vomitus was expelled or not, it is recorded as vomiting in the tables. In some cases no significance was attached to the usual signs of nausea because the experiment was carried out during very hot weather when the animal often panted, licked, and swallowed even when drugs were not given. The occurrence of vomiting during the night could be detected the following morning by a pool of vomitus. It is possible that retching (without the expulsion of vomitus) could have occurred during the night in the case of some animals recorded as having failed to vomit after a given injection. We have, nevertheless, recorded it as a failure to vomit in cases in which vomiting did not occur for some hours of observation after the intravenous injection and in which no evidence of it was detected the following morning. Occasionally an animal may vomit for the first time a few hours after the intravenous injection of the digitalis bodies; especially is this so in

*All doses were given in milligrams per kilogram but "per kilogram" is omitted in the text for the sake of brevity.

the case of digitoxin. Nevertheless, the change in the behavior of the vomiting reflex after repeated injections is sufficiently striking to illustrate the matter under investigation.

The development of "conditioned" vomiting demanded some attention since the animals were made to vomit from drugs at the same place and under the same conditions for several days in succession. We have found that some dogs develop this conditioned reflex after a few days, which may then persist for months. An animal so "conditioned" may begin to lick and swallow when placed on the table and may vomit by the time the electrodes are applied. In these experiments, therefore, the animals were allowed to remain on the table for some time before the injections were made in order to detect such reactions.

RESULTS

The experiments on cats will not be reviewed in detail inasmuch as there were no electrocardiographic records of cardiac changes. With the doses used five of the fifteen experiments demonstrate definite interference with the vomiting reflex after repeated injections of the digitalis bodies. The different experiments varied widely in the number, the size, and the intervals between the individual doses. The following condensed protocol of one experiment will illustrate, however, the type of reaction from which it was deduced that an interference with the vomiting reflex had occurred.

Cat, female, weight 1.32 kg.

October 8	
2:48	0.1 mg. digitoxin per kg. intravenously.
2:50	Falls on side.
3:13	Nausea.
3:15	Vomits.
5:20	Has vomited seven times.
October 10	
2:35	Slight depression; drinks water.
2:37	0.1 mg. digitoxin per kg. intravenously.
3:03	Vomits.
3:47	Vomits.
3:57	General depression.
October 11	
12:54	Slight depression; drinks water.
1:03	0.03 mg. digitoxin per kg. intravenously.
1:26	Refuses water and meat.
3:10	General depression but able to stand and walk about.
6:30	Still no vomiting; general condition same.
October 12	
9:00	Found dead this morning. No signs of vomiting during night. Autopsy—no evidence of infection.

Of the six experiments with dogs the results in five will be presented in some detail in order to convey an idea of the variety of conditions under which the phenomenon under consideration may appear. Summaries are given in Tables I to V. In the case of the sixth animal, vomiting occurred after each of the three daily injections of digitalis and fifteen minutes after the last dose the respiration ceased, although the heart continued to beat while artificial respiration was maintained for an hour. This behavior is atypical and does not show any interference with the vomiting reflex.

TABLE I

DATE	TIME	DOSE PER CENT OF FATAL		NAUSEA AND VOMITING	ONSET IN MINUTES	CARDIAC CHANGES
		SINGLE	TOTAL			
May 8	3:06	33	33	Vomiting	13	Temporary change in focus of pacemaker
May 9	3:31	17	50	Nausea	1	
				No vomiting	--	Normal rhythm
	4:14	17	67	Vomiting	11	Bradycardia
	4:51	Apomorphine HCl				Sinus tachycardia →
		0.5 mg., muscle		No vomiting	--	ventricular tachycardia
	5:09	Apomorphine HCl		Nausea?	--	
		1.0 mg., muscle		No vomiting	--	Sinus tachycardia
May 10	3:08	--	--	--	--	Normal rhythm, slight depression of R-T segment
	3:09	Apomorphine HCl		Nausea	2	
		0.5 mg., muscle		No vomiting	--	Sinus tachycardia
	3:25	17	84	No vomiting	--	Rhythm normal, greater depression of R-T segment
	3:39	17	100	Vomiting	4	Bradycardia → ventricular tachycardia
May 11	9:00	--	--	--	--	Found dead

Dog, male, 7.0 kg. Tr. digitalis was used diluted with an equal volume of normal saline solution after evaporation of alcohol with moderate heat. Doses are stated above in percentage of the total fatal dose for this animal.

EXPERIMENT I.—This experiment lasted three days; the results are presented in Table I. Thirty electrocardiograms were taken during this period, ten of which are reproduced in Fig. 1, and represent the essential cardiac changes. On the first day, one-third of the total dose of digitalis which proved fatal for this animal was injected intravenously. This produced vomiting but no persistent changes in the electrocardiogram (Tracings 1 and 3). The following morning the dog appeared fairly normal, but was still nauseated and refused food and water. A second injection consisting of one-sixth of the fatal dose was made, which caused slowing of the sinus rate and marked nausea but no vomiting (Tracing 11). After a third injection, one-sixth of the fatal dose, the animal became very ill; there was profound slowing of the heart rate, severe nausea, repeated vomiting, respiratory distress, and excitement. When this disturbance had partially subsided, the electrocardiogram appeared practically as it had before any digitalis had been given (Tracing 16). On the morning of the third day the animal was only slightly depressed. An injection of digitalis, one-sixth of the fatal dose, caused a marked depression of the R-T segment but *no nausea or vomiting* (Tracing 25), although by now a total of 84 per cent of the fatal dose of the drug had been

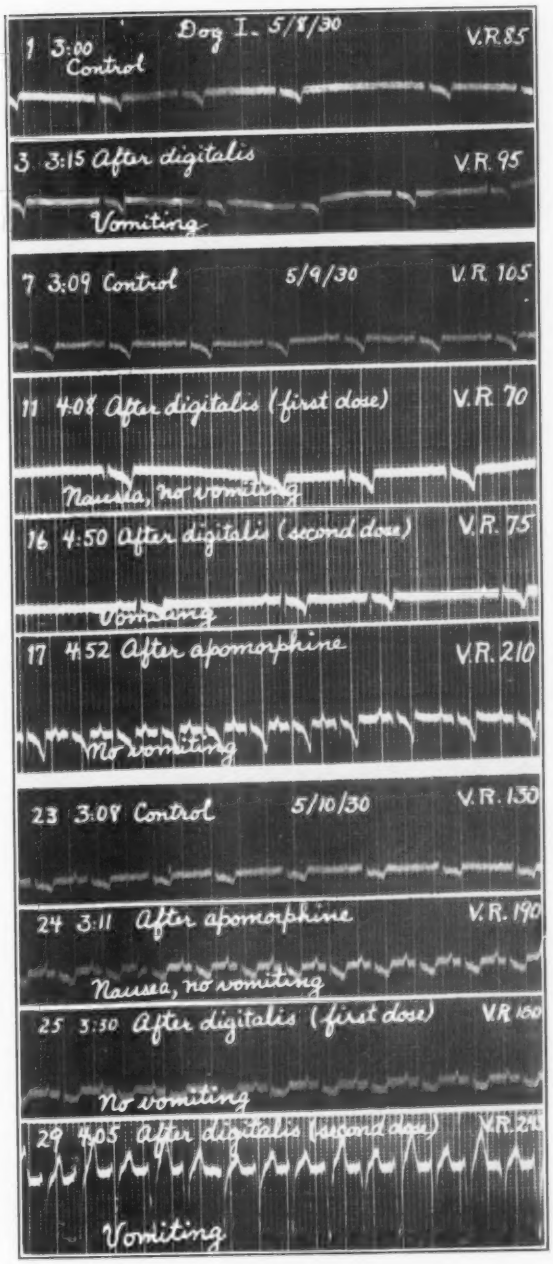
Dog I. 5/8/30
1 3:00 Control V.R. 85
3 3:15 After digitalis V.R. 95
Vomiting
7 3:09 Control 5/9/30 V.R. 105
11 4:08 After digitalis (first dose) V.R. 70
Nausea, no vomiting
16 4:50 After digitalis (second dose) V.R. 75
Vomiting
17 4:52 After apomorphine V.R. 210
No vomiting
23 3:08 Control 5/10/30 V.R. 130
24 3:11 After apomorphine V.R. 190
Nausea, no vomiting
25 3:30 After digitalis (first dose) V.R. 150
No vomiting
29 4:05 After digitalis (second dose) V.R. 24
Vomiting

Fig. 1.

given. The repetition of this dose resulted in the same type of symptoms as occurred after the second dose on the day previous, namely, repeated vomiting, marked respiratory distress, and depression. In addition, however, a ventricular tachycardia was now produced (Tracing 29). The animal was found dead the following morning, and autopsy showed no signs of infection.

Repeated injections of digitalis, therefore, produced progressively increasing poisoning of the heart which was not consistently reflected in the symptom of vomiting. For example, after 33 per cent of the fatal dose vomiting occurred, but the R-T segment was not altered; while after 84 per cent, vomiting was absent although this amount of digitalis was sufficient to produce marked depression of the R-T segment.

After 67 per cent of the fatal dose of digitalis had been given, 1.5 mg. apomorphine then failed to cause emesis, and 0.5 mg. apomorphine before the digitalis on the following day was also ineffective. Since the average minimum intramuscular emetic dose of apomorphine in the dog is about 0.02 mg., there can be no question of the increased threshold of the vomiting reflex to apomorphine in this case. That the apomorphine had been rapidly absorbed is evident from the fact that the injection was followed in two minutes by marked acceleration of the heart rate (Tracings 17 and 24) while the animal was lying perfectly quiet.

TABLE II

DATE	TIME	DOSE	NAUSEA AND VOMITING	ONSET IN MINUTES	CARDIAC CHANGES
May 9	11:48	60% c.u. Digitalis	Nausea	1	Normal rhythm
			Vomiting	5	
May 11	10:15	Apomorphine HCl 0.25 mg., muscle	Vomiting	4	Normal rhythm
May 19	2:57	Ouabain	Nausea	2	Ventricular
		0.05 mg., vein	Vomiting	8	tachycardia
	4:00	Apomorphine HCl 0.25 mg., muscle	Vomiting	4	Ventricular tachycardia
May 20	12:00	--	--	--	Sinus tachycardia
	12:20	Ouabain	No nausea	--	Ventricular tachy-
		0.05 mg., vein	No vomiting	--	cardia in three minutes
	12:37	--	--	--	Convulsion; death

Dog, female, 24.8 kg. c. u. (cat units). Tincture digitalis was used, diluted with an equal volume of normal saline after the alcohol was evaporated off with moderate heat. A solution of ouabain in normal saline 1 in 1000 was used.

EXPERIMENT II.—The results of this experiment are summarized in Table II. Twenty-five electrocardiograms were taken, and the essential tracings are reproduced in Fig. 2. The first dose of digitalis induced salivation and vomiting in five minutes, and after a temporary sinus tachycardia (Tracing 3), the electrocardiogram became entirely normal (Tracing 7). Subsequently 0.05 mg. ouabain caused vomiting in eight minutes and, in addition, a ventricular tachycardia (Tracing 17). The following day the dog refused food but took a large quantity of water which was promptly regurgitated. There was no further nausea or vomiting, although salivation appeared before the next injection. The animal was somewhat less lively than normal but not markedly depressed. There was a sinus tachycardia (Tracing 22). After the dose of ouabain on this day respiration remained unchanged, slight drowsiness was induced, and a ventricular tachycardia appeared (Tracings 23 to 25) which progressed to ventricular fibrillation. This, in turn, was followed by a convulsion and death. The last dose of ouabain had produced a toxic action on the

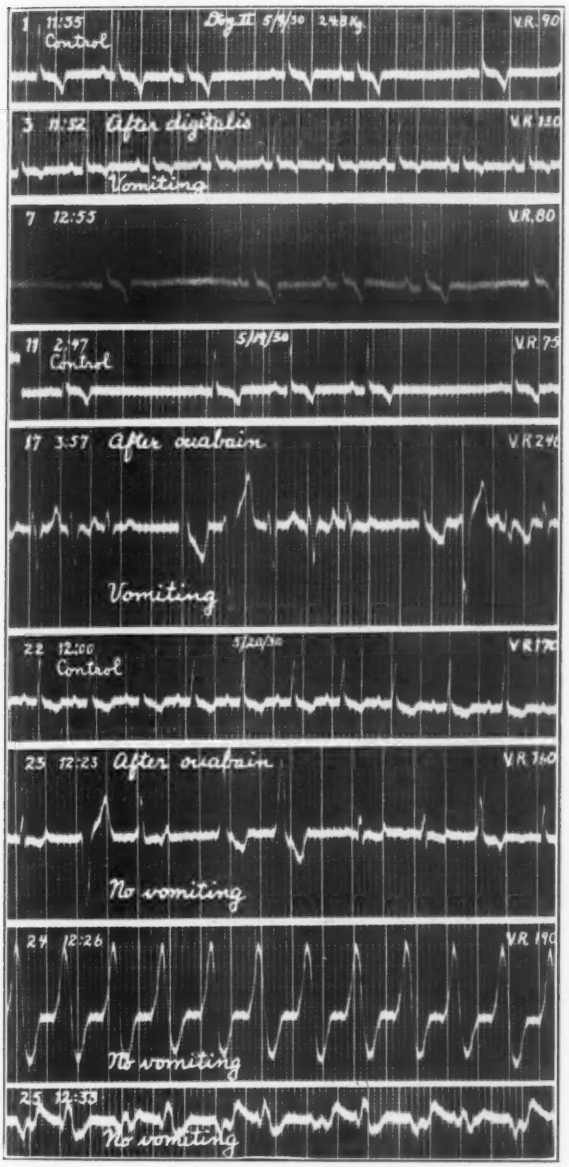
1 11:35 Control
Dog II 5/9/30 24.8 Kg.
V.R. 90
3 11:52 After digitalis
V.R. 130
Vomiting
7 12:55
V.R. 80
11 2:47 Control
5/9/30
V.R. 75
17 3:57 After ouabain
V.R. 240
Vomiting
22 12:00 Control
5/22/30
V.R. 170
25 12:25 After ouabain
V.R. 760
No vomiting
29 12:26
V.R. 190
No vomiting
25 12:38
No vomiting

Fig. 2.

heart without the slightest signs of nausea or vomiting although seventeen minutes had elapsed between the injection and death.

The first injection of ouabain caused vomiting five times in a period of thirty-five minutes. An intramuscular injection of 0.25 mg. apomorphine given twenty-five minutes later promptly produced vomiting which recurred six times. This response was essentially the same as that obtained by a previous control injection of apomorphine.

TABLE III

DATE	TIME	SINGLE DOSE MG./KG.	TOTAL DOSE IN % OF FATAL	NAUSEA AND VOMITING	ONSET IN MINUTES	CARDIAC CHANGES
May 20	4:41	0.025	16.7	Nausea	1	Normal rhythm
	4:54	0.025	32.4	Nausea	1	Normal rhythm
				Vomiting	4	
May 21	12:11	0.025	49.1	Nausea	5	Normal rhythm
				Vomiting	6	
	3:15	0.025	65.8	Vomiting (atypical)	11	Ventricular tachycardia
May 22	9:00	--	--	--	--	Periods of ventricular tachycardia, sinus tachycardia, prolonged P-R intervals
	9:45	0.008	71.1	No nausea	--	Same as above
				No vomiting	--	
	1:41	0.008	76.4	No nausea	--	Sinus bradycardia, ventricular ectopic beats
				No vomiting	--	
	2:04	0.008	81.7	Nausea	3	Ventricular tachycardia
				Vomiting (atypical)	5	
	2:51	Apomorphine HCl 0.25 mg., muscle		Nausea	2	Ventricular tachycardia
				Vomiting	6	
May 23	9:39	--	--	--	--	Ventricular tachycardia
	9:43	0.008	87.0	No nausea	--	Ventricular tachycardia
				No vomiting	--	
	10:23	0.006	91.0	No nausea	--	Ventricular tachycardia
				No vomiting	--	
	10:35	0.012	100.0	No nausea	--	Ventricular tachycardia
				No vomiting	--	
	10:55	--	--	--	--	Ventricular fibrillation; convulsion; death

Dog, male, 12.7kg. A solution of ouabain in normal saline 1 in 1000 was used.

EXPERIMENT III.—The duration of this experiment was four days during which thirty-three electrocardiograms were taken. The results are summarized in Table III and the essential tracings given in Fig. 3.

The first dose of ouabain (16.7 per cent of the fatal) caused nausea, and the same dose given thirteen minutes later induced vomiting in four minutes, which was repeated ten times in the following thirty-seven minutes. The electrocardiograms of this day showed no abnormal rhythm (Tracings 2 and 6), and the animal showed no depression.

The following morning it was evident that the animal had vomited several times during the night. Food was refused, but the dog drank a large quantity of water and appeared fairly normal. The electrocardiogram showed an essentially normal rhythm (Tracing 11) which remained unchanged after the next injection of ouabain (16.7 per cent of the fatal dose) (Tracing 14). This dose also caused vomiting which was repeated six times. The repetition of this dose nearly two hours after vomiting had stopped produced a ventricular tachycardia (Tracing 17), in addition

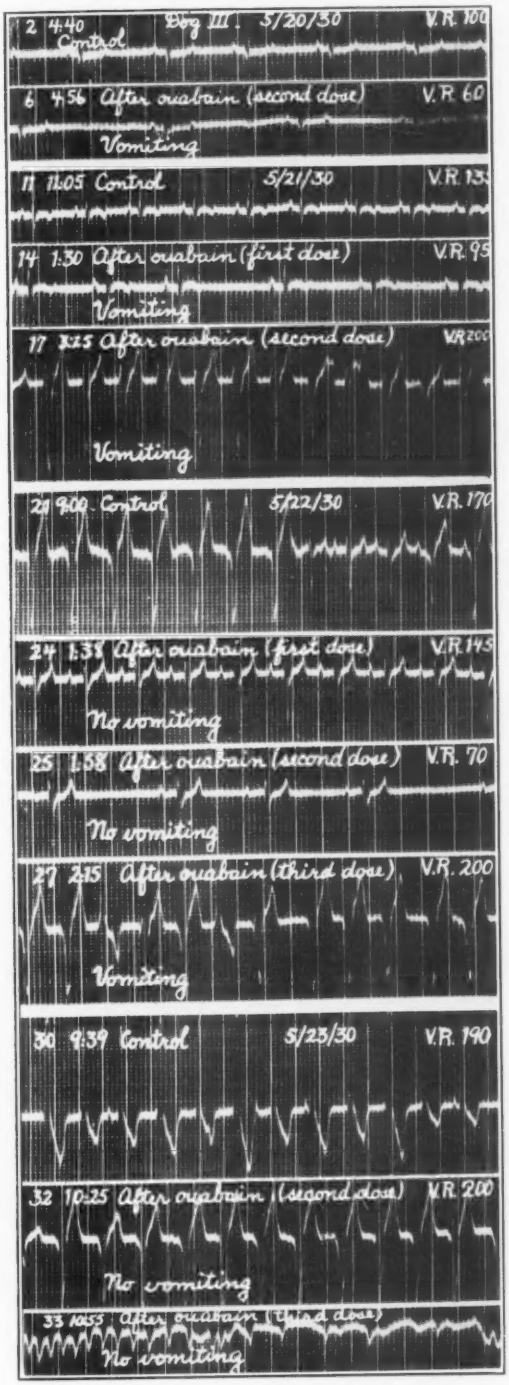
2 4:40 Control Dog III 5/20/30 V.R. 100
6 4:56 After ouabain (second dose) V.R. 60
Vomiting
11 11:05 Control 5/21/30 V.R. 13
14 1:30 After ouabain (first dose) V.R. 95
Vomiting
17 2:15 After ouabain (second dose) V.R. 200
Vomiting
21 9:00 Control 5/22/30 V.R. 170
24 1:33 After ouabain (first dose) V.R. 145
No vomiting
25 1:58 After ouabain (second dose) V.R. 70
No vomiting
27 2:15 After ouabain (third dose) V.R. 200
Vomiting
30 9:39 Control 5/23/30 V.R. 190
32 10:25 After ouabain (second dose) V.R. 200
No vomiting
33 10:55 After ouabain (third dose)
No vomiting

Fig. 3.

to a severe generalized disturbance that was characterized by slow, deep, and gasping respiration and violent excitement in which the animal threw itself about and cried out. Repeated atypical retching movements ensued. Considerable restlessness and marked weakness lasted for more than an hour and a half, after which the animal showed improvement and drank a large amount of water.

On the morning of the third day, there was no evidence of vomiting during the night. The animal appeared slightly weak, but again drank a large quantity of water. The electrocardiogram showed long periods of ventricular tachycardia (Tracing 21). Two doses of ouabain (each 5.3 per cent of the fatal) produced further cardiac changes but no vomiting (Tracings 24 and 25). A third dose induced an attack similar to that on the previous day, with extreme respiratory distress and atypical retching (Tracing 27). After partial recovery from this, the animal was capable of vomiting from apomorphine.

On the morning of the fourth day, there was again no sign of vomiting during the night. The animal was slightly depressed, and drank a considerable quantity of water but refused food. The electrocardiogram showed ventricular tachycardia (Tracing 30). Three doses of ouabain were injected but produced neither vomiting nor even signs of nausea. The last of these doses caused another severe attack of excitement and respiratory distress, the animal biting at the chain, clawing violently at its mouth, belching, and grunting. There was partial recovery in about fifteen minutes, but as the animal was lifted from the floor and placed on the table, a convulsion occurred and the electrocardiogram showed ventricular fibrillation (Tracing 33). On this day, although a dose of ouabain had been given which produced fatal poisoning of the heart, there was neither nausea nor vomiting.

TABLE IV

DATE	TIME	DOSE MG./KG.	VOMITING	ONSET IN MINUTES	CARDIAC CHANGES
June 6	1:49	0.10	Vomiting	26	Normal rhythm
	3:48	0.05	Vomiting	12	Normal rhythm
June 7	10:15	0.05	No vomiting	--	Normal rhythm
	11:10	0.05	Vomiting	7	Normal rhythm
June 9	1:50	0.10	No vomiting	--	Normal rhythm
	2:52	0.10	Vomiting	8	Normal rhythm
June 10	11:21	0.10	No vomiting	--	Normal rhythm
	12:57	0.05	No vomiting	--	Normal rhythm
	2:17	0.10	No vomiting	--	Normal rhythm
	3:47	0.10	No vomiting	--	Ventricular ectopic beats
	4:40	Apomorphine HCl 1 mg., muscle	Vomiting	3	Normal rhythm
June 11	12:14	0.15	No vomiting	--	Ventricular ectopic beats
	1:33	0.15	No vomiting	--	Ventricular ectopic beats
	2:34	0.15	No vomiting	--	Ventricular tachycardia
	3:34	Apomorphine HCl 0.25 mg., muscle	No vomiting	--	Ventricular tachycardia
	3:50	Apomorphine HCl 0.25 mg., vein	No vomiting	--	Ventricular tachycardia
	4:00	Apomorphine HCl 0.50 mg., muscle	Vomiting	3	Ventricular tachycardia
June 12	11:25	0.15	Vomiting	49	Ventricular tachycardia
	3:35	Picrotoxin-like convulsions	----	--	Ventricular tachycardia
	4:10	Death			

Dog, male, 18.2 kg. A solution of Digitoxin-Merck was used, containing 10 mg. in 1 c.c. alcohol and diluted ten times with normal saline for injection.

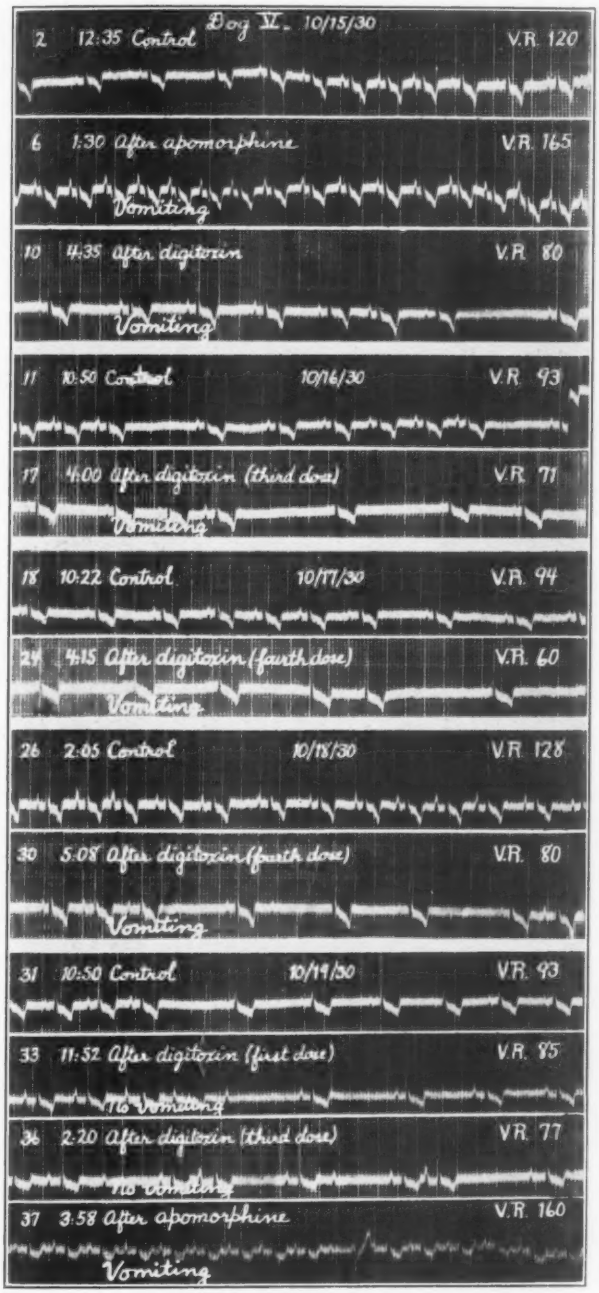
Dog V. 10/15/30
2 12:35 Control V.R. 120
6 1:30 After apomorphine V.R. 165
Vomiting
10 4:35 After digitoxin V.R. 80
Vomiting
11 10:50 Control 10/16/30 V.R. 93
17 4:00 After digitoxin (third dose) V.R. 71
Vomiting
18 10:22 Control 10/17/30 V.R. 94
24 4:15 After digitoxin (fourth dose) V.R. 60
Vomiting
26 2:05 Control 10/18/30 V.R. 128
30 5:08 After digitoxin (fourth dose) V.R. 80
Vomiting
31 10:50 Control 10/19/30 V.R. 93
33 11:52 After digitoxin (first dose) V.R. 85
No Vomiting
36 2:20 After digitoxin (third dose) V.R. 77
No Vomiting
37 3:58 After apomorphine V.R. 160
Vomiting

Fig. 4.

EXPERIMENT IV.—In this experiment fifty-five electrocardiograms were taken. None are reproduced, since the tracings are essentially the same as those of Experiment III. The relation between the repeated injections of digitoxin and the occurrence of vomiting is shown in Table IV. It may be seen that emesis occurred after the total dose given on each of the first three days (June 6, 7, and 9). On the next two days (June 10 and 11) even larger doses failed to cause vomiting, although a greater toxic action on the heart was in evidence, namely, ventricular tachycardia. On the following day (June 12) an injection caused vomiting and death. Thus, a progressive increase in the threshold of the vomiting mechanism is shown. On the first day, 0.1 mg. digitoxin caused vomiting. On the third day (June 9), 0.1 mg. was no longer effective, while 0.2 mg. still induced emesis. On the fourth day, even after 0.35 mg., vomiting did not occur. On the fifth day, 0.45 mg. was also insufficient to cause vomiting. On the last day, a dose of 0.15 mg. produced vomiting, but by this time sufficient cumulation had taken place for this small dose to cause death.

TABLE V

DATE	TIME	DOSE MG./KG.	NAUSEA AND VOMITING	ONSET IN MINUTES	CARDIAC CHANGES
Oct. 15	1:15	Apomorphine HCl	Nausea	1	Sinus tachycardia
		0.05 mg., vein	Vomiting	1	
	3:21	0.10	Nausea	3	Sinus slowing
			Vomiting	34*	
Oct. 16	11:00	0.05	No nausea	--	Sinus slowing
			No vomiting	--	
	11:58	0.05	Nausea	1	Sinus slowing
			Vomiting	44	
	1:48	0.05	Nausea	½	Sinus slowing
			Vomiting	2	
Oct. 17	10:30	0.05	Nausea	1	Normal rhythm
			No vomiting	--	
	12:05	0.05	No nausea	--	Sinus slowing
			No vomiting	--	
	1:10	0.05	Nausea	5	Sinus slowing
			Vomiting	6	
	2:10	0.05	Vomiting	130†	Sinus slowing
Oct. 18	2:07	0.05	No nausea	--	Sinus slowing
			No vomiting	--	
	3:07	0.05	No nausea	--	Sinus slowing
			No vomiting	--	
	4:07	0.05	Nausea	3	Sinus slowing
			Vomiting	4	
	4:52	0.10	Nausea	3	Dropped beats
			Vomiting	23‡	
	10:53	0.10	Nausea	47	Dropped beats
			No vomiting	--	
	12:00	0.05	Nausea	25	Dropped beats
			No vomiting	--	
	1:12	0.05	Nausea	6	More frequent dropped beats
			No vomiting	--	
	3:00	Apomorphine HCl	Nausea	3	Sinus tachycardia with A-V block
Oct. 19		0.05 mg., vein	Vomiting	23	

Dog, male, 7.6 kg. A solution of Digitoxin-Merck was used, continuing 10 mg. in 1 c.c. alcohol and diluted ten times with normal saline for injection.

*After preliminary nausea ate meat ravenously and then had nausea and vomiting twenty minutes later.

†In this case there were no signs of nausea or vomiting while the animal was lying on the table, but when placed on the floor, it vomited almost instantly.

‡Vomited again only after being placed on the floor, not while sitting on the table. Neither in this case nor in that above was the animal lying on its back, nor in any way restrained.

When the animal began to show resistance to the emetic action of digitoxin, it was also resistant to that of apomorphine. An intramuscular injection of 0.25 mg. apomorphine and a similar dose given intravenously sixteen minutes later proved ineffective. An additional dose of 0.5 mg. intramuscularly produced vomiting in three minutes.

EXPERIMENT V.—This experiment was conducted for five days. Thirty-seven electrocardiograms were taken. The essential facts are summarized in Table V and illustrated by the tracings in Fig. 4. The animal vomited from the digitoxin injections on each of the first four days but failed to do so after the digitoxin on the fifth day. So far as the cardiac poisoning is concerned, the dose that produced vomiting on the first day was insufficient to cause heart-block (Tracing 10). On the other hand, vomiting was absent on the fifth day after a total quantity of the drug that was sufficient to produce heart-block (Tracings 33, 36, and 37). It is interesting to compare Tracings 6 and 37. Each shows the sinus tachycardia following apomorphine. Tracing 6, however, is otherwise normal, the P-R intervals being 0.04 to 0.06 second, while Tracing 37 shows in addition to the sinus tachycardia a marked toxic action of digitoxin, namely, P-R intervals 0.10 to 0.12 second, dropped beats, a ventricular ectopic beat, and marked depression of the R-T segment. After Tracing 6, digitoxin produced emesis without any electrocardiographic signs of toxicity, while at the time that Tracing 37 was taken there was marked resistance to the emetic action of digitoxin.

DISCUSSION

The experiments of the present study set forth the fact that after repeated doses of the digitalis bodies the vomiting reflex in the dog and the cat shows a change in the reaction to the drug. This change is such that a dose previously effective in producing vomiting becomes ineffective. The cardiac poisoning continues to increase progressively with the repeated doses so that ultimately a toxic rhythm without emesis is induced by an additional dose of the drug which at the beginning of the experiment caused vomiting without the toxic rhythm. This is perhaps the most significant fact of this study, because vomiting is generally relied upon clinically as a signal for the discontinuation of the drug in order to avoid serious cardiac poisoning.

The explanation of the foregoing phenomenon brings up many possibilities, such as (1) fatigue of the vomiting reflex due to prolonged vomiting, (2) general depression of the animal, (3) suppression of the vomiting reflex by a stronger impulse arising from the sudden disorder of the cardiac rhythm, (4) differences in the degree of fixation of the drug by different structures, (5) the development of tolerance to digitalis by the structures concerned with vomiting, (6) direct depression of the vomiting reflex by the digitalis bodies.

Fatigue of the vomiting reflex as the result of prolonged vomiting suggested itself because toxic doses of digitalis cause very severe vomiting that may last several hours and even days. In some cases, the animal vomited as many as ten or fifteen times after each injection. It is well known, however, that the vomiting reflex recovers very

rapidly. Patients are often seen to vomit many times daily for weeks without signs of fatigue of this reflex, and in experiments with the daily injection of apomorphine in dogs we have seen no sign of fatigue of this mechanism after vomiting many times following each dose for a period of ten days or longer.

General depression of the animal can be dismissed as playing no rôle of importance in the failure to produce vomiting by digitalis in these experiments. When the heart was poisoned by large doses of the drug and the animal had refused food for three or four days, there was some weakness and general depression. At the time when the reflex began to show a change in its response to the drug, however, the general depression was in no case extreme, for the animals could stand up and walk about and in some instances drank water.

It seemed possible that an abnormal impulse arising from the heart as the result of the sudden onset of an extremely toxic cardiac rhythm might interfere with the vomiting reflex, for there are many familiar examples of the suppression of one reflex act by another. This factor, however, could not have played any considerable rôle in these experiments because in some instances severe disorders of cardiac rhythm occurred before the animal showed any interference with the vomiting reflex, while in other cases interference with this reflex was observed before any serious disorder of cardiac rhythm was in evidence.

That differences in the degree of fixation of the drug by different cardiac structures might be an explanation of the above phenomenon was suggested particularly by the observations of Experiment I. In this case the first dose consisting of 33 per cent of the fatal, induced vomiting. On each of the next two days approximately the same doses were necessary to induce vomiting. The fact that the animal died after the third day shows that progressive cumulation had taken place. But the fact that the same dose was required each day to induce vomiting suggested further that cumulation was not taking place in the structures concerned with the vomiting reflex. This view, however, becomes untenable in the light of the well-known fact that vomiting from a large dose of digitalis may last for hours and even days. It would fail to explain the fact that in some instances after repeated injections, single doses larger than those which at first caused vomiting now failed to produce it.

The development of tissue tolerance by some structure of the vomiting reflex would explain the observation that larger doses of digitalis become necessary to induce vomiting after repeated injections. There is no evidence, however, that any other cardiac structure can develop tolerance to digitalis. Furthermore, it would be extraordinary if a specific tolerance developed to digitalis were to extend to such a totally

different drug as apomorphine, inasmuch as the animal rendered resistant to digitalis may also become resistant to apomorphine.

The most probable explanation of the change in the response of the vomiting reflex appears to be that repeated cumulative doses of digitalis may continue to increase the cardiac poisoning while at the same time directly depressing the vomiting reflex. This rise in the threshold of the vomiting reflex may entirely abolish the emetic action of further doses of the drug (Tables II and III). An effort was made to determine whether this elevation of the threshold to stimulation might be induced by repeated small doses without ever causing vomiting, until a fatal dose had been injected, in somewhat the same way as morphine in small repeated doses may depress the vomiting center without ever causing vomiting. We cannot state whether this is possible in the case of the digitalis bodies, for with the doses employed in these experiments vomiting always occurred for the first time after the administration of only small fractions of the total quantities that proved fatal in the course of several days.

The increase in the threshold to stimulation by digitalis is not specific for that drug, but applies also to apomorphine. In Experiment I, seventy-five times the minimal emetic dose of apomorphine given intramuscularly failed to cause vomiting at a time when the animal had become resistant to vomiting by digitalis. In Experiment IV, when the vomiting mechanism became resistant to digitoxin so that nearly five times the previous emetic dose was ineffective, the animal was still capable of vomiting promptly from apomorphine. In this case, however, much larger doses than normally were required, for about twelve times the minimal intramuscular emetic dose and more than twelve times the minimal intravenous emetic dose given sixteen minutes later failed to cause vomiting. In the remaining experiments there was no evidence of increased tolerance to apomorphine. The doses, however, were too large to permit the detection of slight degrees of tolerance if any had developed. The fact that in two experiments the animals failed to vomit from such large doses of apomorphine leaves little doubt that repeated injections of the digitalis bodies rendered the reflex resistant to stimulation not only by these drugs but by apomorphine as well.

Our experiments afford no direct evidence for the exact seat of this depression of the vomiting reflex. In view of the recent studies[3] which indicate that digitalis vomiting results from stimulation of peripheral endings in the heart, it seems probable that the depression of this reflex is also due to a peripheral action. The fact that the depression applies to apomorphine as well indicates that not only the cardiac fibers, but also other peripheral fibers are depressed by digitalis. Hatcher and Weiss[4] have shown that the digitalis bodies may stimulate peripheral nerve fibers other than those in the heart.

In man, gastrointestinal disturbances are usually the first indications of digitalis poisoning. It is not uncommon, however, for abnormal cardiac rhythms (premature beats, bigeminy, block) to appear as the initial signs of toxicity. It is also observed that patients who are receiving large doses of digitalis die occasionally under conditions which suggest that the drug may have been responsible for the fatality, although nausea and vomiting were absent. For example, in the recent study on digitalis therapy in lobar pneumonia reported by Wyckoff, Du Bois, and Woodruff,[5] it was found that patients receiving digitalis showed a higher mortality (41.4 per cent) than those who were not treated with the drug (33.7 per cent), and furthermore, that the highest mortality (64.2 per cent) occurred in that group which at no time showed nausea or vomiting, although very large doses of the drug were administered. This observation is not strictly analogous to those of the present experiments, although it is conceivable that the pneumonia or the large doses of the drug or both, may have produced depression of the vomiting reflex which rendered it resistant to the usual action of digitalis. As we have already mentioned, animals have occasionally been observed to die without vomiting following a single large intramuscular injection of ouabain.

The clinical observations that bear more closely upon the results of the present study are the following: patients sometimes vomit from the toxic action of digitalis, and then as the drug is continued, vomiting ceases and other toxic effects appear in the form of frequent premature contractions or a bigeminal rhythm. There are several possible explanations for such changes. It is probable that active carditis and the progressive myocardial failure of the terminal stages of heart disease, both of which render the heart more susceptible to toxic rhythms produced by digitalis,[6] may explain these observations in some instances. The experiments of the present study deal with intense poisoning of the heart and it is not possible at present to state how frequently such conditions are duplicated in the clinical use of the digitalis bodies. It will, however, be well to bear in mind the fact established in these animal experiments, that the continued administration of large doses of these drugs may depress the vomiting reflex while progressively increasing the intensity of the cardiac poisoning, and that, after an initial period of vomiting under these conditions the digitalis bodies may even cause death without further vomiting.

CONCLUSION

Repeated doses of the digitalis bodies may depress the vomiting reflex while simultaneously increasing the intensity of the cardiac poisoning, so that after an initial period of vomiting the continued administration of these drugs may fail to produce emesis and may even

cause death without further vomiting. These experimental results suggest the need of caution in relying upon nausea and vomiting as measures of the degree of cardiac poisoning in the clinical use of the digitalis bodies.

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EOSINOPHILIA DUE TO THE ADMINISTRATION OF DIGITALIS*

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IN THE foreign literature, a few cases have been reported in which the administration of digitalis or its derivatives has been associated with a definite increase in the number of eosinophiles in the circulating blood.

Recht[1] records the study of a series of patients who had received digitalis (the powdered leaf and digipuratum) to the point of producing nausea, bradycardia, and other minor toxic symptoms. He states that on the average an eosinophilia of 6 to 8 per cent was observed. There were, however, in his series two outstanding cases which showed an eosinophilia of 18 to 20 per cent and 12 per cent, respectively. The first of these was a woman of fifty-six years with congestive heart failure who had been without digitalis for four weeks before admission to the hospital. Her eosinophile count on admission is not stated. She was given large doses of digitalis, and on the second day after admission, had an eosinophile count of 18 to 20 per cent. At this time digestive disturbances, bradycardia, and bigeminy indicated cessation of digitalis administration. While digitalis was withheld, the eosinophile count dropped gradually to 5 or 6 per cent, and remained at this level for several weeks. After two months, it was again necessary to give digitalis. The eosinophile count increased slowly to 9 per cent and at the end of three weeks reached 12 per cent. The second case, similarly treated, showed a maximum count of 12 per cent under digitalis therapy. Recht attributes this increase of eosinophile cells in the blood to the stimulation of the vagus or autonomic nervous system by the vagotropic drug, digitalis. Other causes for eosinophilia were considered to have been excluded in his cases.

Braun[2] reports a case of congestive failure with edema, in which an "eosinophilia" the degree of which is not stated, occurred during digitalis administration. Braun attributes this to a foreign protein reaction due to absorption of the edema fluid.

On the other hand, N. Diakoff[7] in a recent report on the therapeutic efficiency of some digitalis grown in Perm, states that while the samples showed satisfactory therapeutic activity, there was no occurrence of eosinophilia in the 14 cases which were studied during administration of the drug.

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The following case of eosinophilia associated with digitalis administration occurred under our observation.

CASE REPORT

The patient was a negro male, thirty-six years old, admitted to the Out-patient Department for the first time in June, 1929. He complained of shortness of breath, cough, and precordial pain. He had had measles and mumps in childhood, and pneumonia in 1926. He had had an attack of rheumatic fever at the age of seven years, and a similar attack each winter until the age of twenty-one. There had been no severe attacks of rheumatism since that time. In February, 1929, nine months before admission, he had an attack of fever with painful and swollen joints, became short of breath, and developed a productive cough. In April, 1929, he began to have edema of the ankles and was in bed for a month. He had been vomiting 1 to 3 times a day and had had nocturia 3 or 4 times a night.

In June, 1929, he entered the Out-patient Department and was treated with digitalis and bed rest at home. He improved temporarily, but after four months developed decompensation and was referred to the hospital.

On October 14, when he entered the hospital, his physical examination showed the heart to be enlarged to the sixth left intercostal space and outside the midclavicular line. There was a blowing systolic murmur at the apex. No diastolic murmur could be heard. The cardiac rhythm was totally irregular with a pulse deficit of 35 beats per minute; B.P. $\frac{120\text{-}90}{70}$. There were râles scattered throughout the lungs. The liver was felt 1 or 2 finger breadths below the costal margin. There was no edema of the extremities.

With bed rest and digitalis in usual amounts, he seemed to regain compensation, though the cough persisted. He was discharged on October 26.

The laboratory findings on this admission were:

White blood cells	10,600
	PER CENT
Polymorphonuclears	67
Lymphocytes	28
Transitional cells	4
Eosinophiles	0
Unclassified	1
Wassermann	negative

He was admitted to the hospital again, one month later. The cough was more severe and there were ascites and edema. He was again treated with digitalis and bed rest. At this time a low diastolic murmur was heard along the left sternal margin. He remained in the hospital until December 18 when he was transferred to another hospital in which he stayed until March, 1930.

The differential blood count on the second admission was:

White blood cells	7,260
	PER CENT
Basophiles	1
Eosinophiles	1
Myelocytes	0
Juveniles	0
Stab cells	1
Segmented cells	69
Lymphocytes	26
Monocytes	2

He was readmitted on our service on April 30 with dyspnea, orthopnea, edema, nausea, vomiting, and distressing cough; B.P. $\frac{180}{100}$. Digitalis was withheld for six days and then commenced again. He improved considerably and was discharged on May 28.

His course was followed through the Out-patient Department and he was readmitted on October 30 on account of incessant cough and decompensation; there was bloating of the abdomen, probably ascites, and edema of the legs. The liver was enlarged and tender. He had been receiving 25 drops of tincture of digitalis three times a day previous to admission. Because he had begun to vomit, it was considered that the patient was showing early symptoms of digitalis intoxication and the drug was stopped.

The laboratory findings at the time of this admission were of special interest.

10/30/30	White blood count	12,000
		PER CENT
	Basophiles	1
	Eosinophiles	9
	Juveniles	0
	Myelocytes	0
	Stab cells	3
	Segmented cells	55
	Lymphocytes	30
	Monocytes	2
11/ 3/30	Blood eosinophiles	26
11/ 7/30	Blood eosinophiles	24
	Sputum contained no eosinophiles.	
	Stool contained no parasites.	

The rapidly rising eosinophile count attracted much attention. An exhaustive search was made for parasitic infection but none could be found. A complement-fixation test for echinococcus was negative. There was no dermatitis or other obvious dermatological condition.

At this time, the literature concerning the relation between digitalis and eosinophilia came to our notice and it was decided to omit digitalis administration as long as possible in order to observe the effect on the differential blood count.

11/13/30	Blood eosinophiles	20 per cent

The patient, who had received no digitalis for two weeks, was beginning to show evidence of increasing decompensation.

11/17/30	Blood eosinophiles	12 per cent
	Stool negative for parasites	
11/19/30	Blood eosinophiles	11 per cent

Dr. L. W. Dean examined the patient at this time and made the following report on his nasal condition. "The nasal mucosa is reddened, the tint being a little darker than normal. The turbinates are of normal size. There is complete absence of the edema which usually characterizes the presence of eosinophiles in the nasal smear." Nasal smear, however, showed:

	PER CENT
Eosinophiles	55
Lymphocytes	31
Polymorphonuclears	14

11/20/30 The patient was showing marked signs of decompensation and it was decided that digitalis therapy should be resumed. He received 8 cat units, or 0.8 gm., of digitalis leaf at 3 P.M. and 4 cat units, or 0.4 gm. more, at 10 P.M.

11/21/30 There was a marked improvement in symptoms and appearance.
Blood eosinophiles 19 per cent

11/23/30 Receiving 0.1 gm. of powdered digitalis leaf per day he felt well.

		PER CENT
	Blood eosinophiles	30
11/25/30	Blood eosinophiles	30
11/30/30	White blood cells	9,750
		PER CENT
	Blood eosinophiles	30
12/ 3/30	Blood eosinophiles	30
12/ 8/30	Blood eosinophiles	30

Upon this maintenance dose of digitalis the eosinophilia was held at a constant level. The compensation of the heart seemed to be restored. The cough diminished. He was able to be up most of the time and although his capacity for exertion was greatly limited, he was discharged on Dec. 13, 1930, with directions to take 60 minims of a tincture of digitalis each day.

Decompensation of the heart began almost immediately after discharge from the hospital and he was readmitted on Dec. 29, 1930. He showed orthopnea, cyanosis, ascites, and edema. The heart sounds were of poor quality and the liver was much enlarged.

Blood eosinophiles 11 per cent

He never rallied after admission. He developed a temperature of 41.2° C., became irrational, stuporous, and finally died on Jan. 3, 1931.

At autopsy the heart showed sclerosis and scarring of the rheumatic type, causing stenosis of the mitral valve and insufficiency of the aortic valve. There was cardiac hypertrophy and chronic myocarditis. Edema of the lungs and chronic passive congestion of the liver, kidneys, and viscera were apparent. No parasites were found.

COMMENT

It is interesting that the patient had been under observation for a year and four months before eosinophilia was noted. Although digitalis had been given on more than one occasion, when the high eosinophile count was first discovered, he had been receiving outside of the hospital what appeared to be a mildly intoxicating dose. The history makes it apparent that no particular preparation of digitalis could be blamed for the eosinophile response which at one time followed a tincture given in the Out-patient Department and at another seemed to be induced by large doses of the powdered leaf.

The relationship of digitalis administration to eosinophilia during the later admissions is shown in Fig. 1.

At the time the blood count was showing a persistent eosinophilia of about 30 per cent (see next to last admission) the patient was sub-

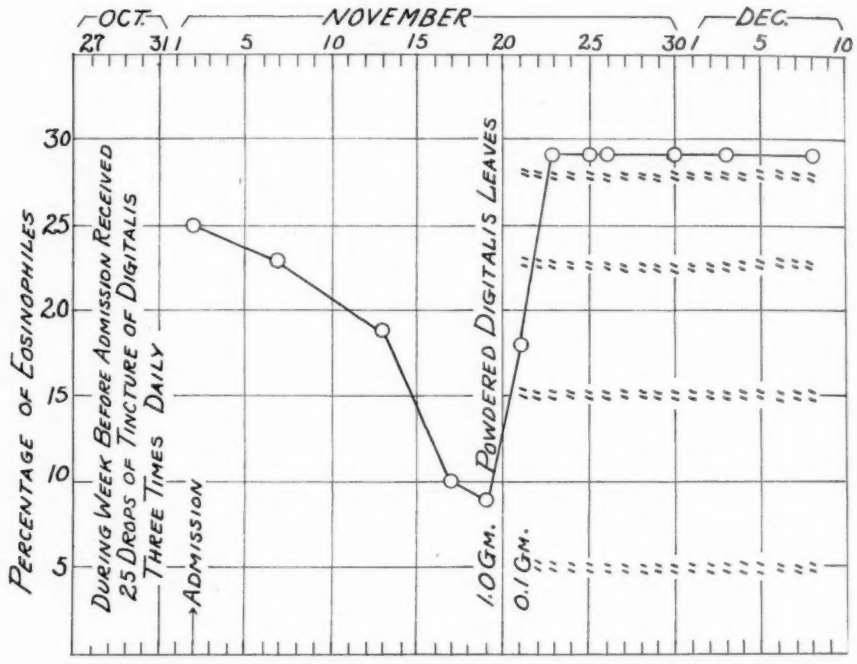

Fig. 1.—Relationship of eosinophilia to digitalis medication, showing apparent response both to tincture of digitalis given before admission and to powdered digitalis leaf administered in the hospital.

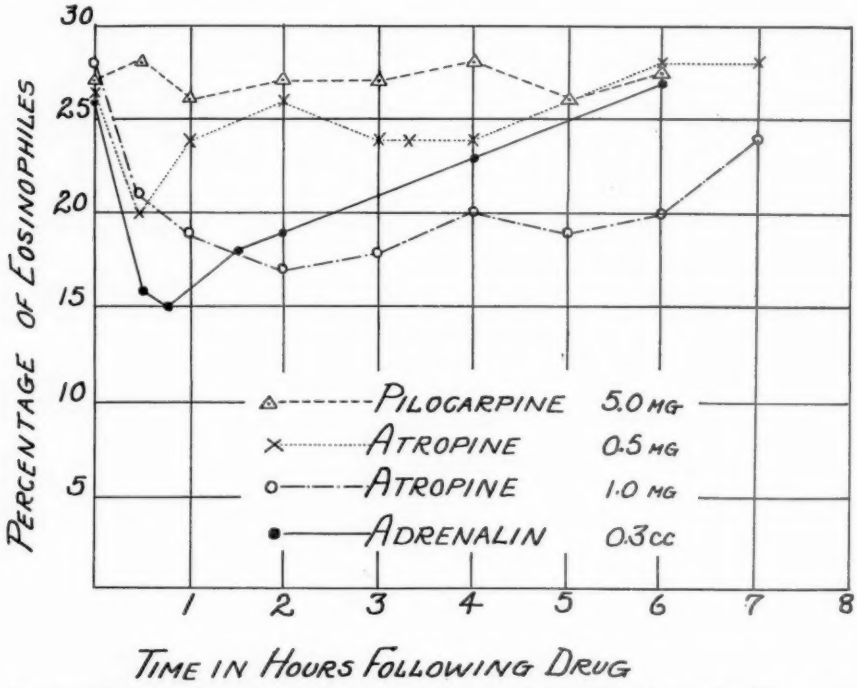

Fig. 2.—The effects of pilocarpine, atropine, and adrenalin on the eosinophile count.

jected to a series of experiments with atropine, adrenalin, and pilocarpine. Clinically, he showed no unusual susceptibility to any of these drugs. The effects on the eosinophile count are shown in Fig. 2.

Pilocarpine was without effect. Adrenalin produced a sharp drop with a gradual rise to the original level. Atropine, in a dose of 0.5 mg., caused a rapid though slight drop with almost immediate return. The effect of 1.0 mg. of atropine was more striking and much more persistent. In seven hours the eosinophilia had not returned to its original level.

Observations were made upon a series of 9 patients with heart disease, all of whom were under the full therapeutic effects of digitalis. In no case was there an eosinophilia of more than 4 per cent. The authors have had verbal reports, however, from Dr. J. F. Bredeek of 3 patients in whom an eosinophilia of 12 to 15 per cent could apparently be attributed to digitalis.

DISCUSSION

The eosinophilic response accompanying digitalis administration would appear to be of infrequent occurrence. It has attracted little attention and is not mentioned in textbooks of blood conditions. Its mechanism is by no means clear.

There is some evidence that the vagus or autonomic system has an influence on the number of eosinophile cells in the blood. A moderate eosinophilia is mentioned by Eppinger and Hess[3] as part of the syndrome of vagotonia. It is also described by Schilling.[4] Eosinophilia has been observed in association with tumors, especially in chest tumors involving the region of the vagus nerves. Hajos, Nemeth, and Enyedy[5] have shown that direct stimulation of the vagus produces an increase of eosinophiles in the blood of experimental animals. Bertellini and Falta[6] have caused an increase of eosinophiles in dogs and man upon administration of pilocarpine and a decrease after giving atropine.

The response of our patient to drugs partially confirms these observations. It is true that pilocarpine caused no change in the eosinophile count. Atropine, however, caused a diminished eosinophilia which after large doses tended to be persistent.

Because it is known that digitalis has an effect on the vagus center, it is somewhat tempting to assume that the eosinophilia is a result of vagal stimulation in a specially sensitive person. In our patient, however, it was not demonstrated that, clinically or from the standpoint of eosinophilic response, there was any unusual sensitiveness to the drugs which most affect the vagus.

SUMMARY

Eosinophilia apparently due to the administration of digitalis is reported. Similar cases in the literature are cited. Observations have

been made on the effect of adrenalin, atropine, and pilocarpine on the eosinophile count. Eosinophilia as an effect of vagus stimulation is briefly discussed. Studies of the blood of 9 other fully digitalized patients revealed no abnormal eosinophilia.

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OBSERVATIONS ON THE DURATION OF THE ELECTRICAL SYSTOLE OF THE HEART, WITH SPECIAL REFERENCE TO THE EFFECT OF DIGITALIS*

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THE significance of changes in the duration of the electrical systole is a problem which still remains to be solved. In the electrocardiogram, we consider as the duration of systole the time interval between the onset of the QRS wave and the end of the T-wave. While this Q-T interval may not exactly correspond to the actual systole of the heart, most authors agree that it is a satisfactory index of its duration and sufficiently accurate for comparative studies.

The first fact which attracts our attention when comparing different electrocardiographic tracings, is the effect of heart rate on the Q-T interval. In cases of bradycardia the Q-T interval is long, while in cases of tachycardia it is short. If we analyze a group of normal tracings, we make the further observation that, while systole shortens with increasing heart rate, diastole does so still more rapidly. For example, at a rate of 50 beats per minute, the Q-T interval will be approximately 0.40 second, the total cardiac cycle about 1.16 seconds; while at a rate of 135 per minute, the Q-T interval will be 0.29 second and the whole cardiac cycle only 0.44 second. In other words, at a rate of 50, systole occupies nearly one third of the cardiac cycle; while at a rate of 135, it fills more than two thirds of the cardiac cycle.

The P-R interval varies with the heart rate in the same manner.

The first one to study the duration of the electrical systole systematically, was Fridericia[5] (1920). From 50 carefully selected normal cases he published a table of normal values for the duration of the Q-T interval at heart rates varying from 50 to 135, and constructed a formula for the determination of the normal average duration of the Q-T interval, which he expresses as follows:

$$S = 8.22 \cdot \sqrt[3]{p}$$

(S = Q-T interval, p = pulse period.)

Fridericia's normal values were confirmed by Miki,[10] Pardee,[17] and P. D. White and S. G. Mudd.[18] Another formula suggested by Lombard and Cope,[2, 16] was proved less reliable by comparative studies of Miki.

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Besides the rate, another factor which has a definite effect upon the duration of the electrical systole is the administration of digitalis. The quantitative measurement of this effect is the object of the present study.

Twenty-one patients with definite cardiac disease, but with regular rhythm were selected. Patients with irregular heart action, especially those with auricular fibrillation, had to be excluded, for in those patients it is impossible to determine accurately the rate per minute from a tracing which shows only 8 to 12 ventricular complexes, and, therefore, it is also impossible to determine the normal value of Q-T for them. Measurements taken from the three different leads of the same patient varied up to 18 per cent, if the direction of T was the same in all of them, and varied still more, if T was inverted in one or two leads. Fridericia observed that with inversion of the T-wave the S-T interval

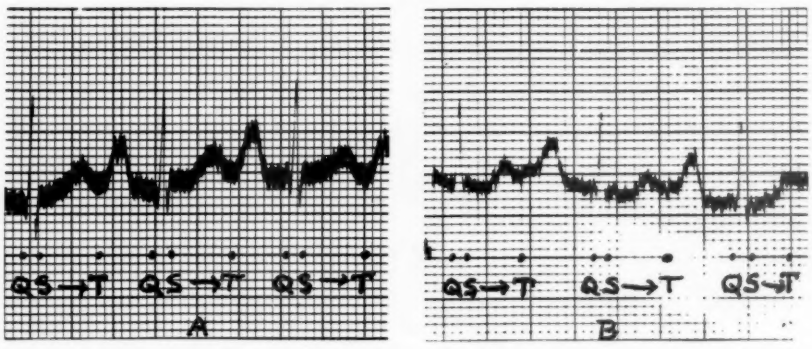

Fig. 1.—Case 10. A, before digitalization; B, after digitalization. The QRS interval was measured first, from the beginning of Q to the end of S. Then the S-T interval was measured, from the end of S to the end of T. The Q-T interval was obtained by the addition of the QRS and the S-T intervals.

was always shorter than with an upright T. This finding is confirmed in the present study. All final measurements were done on Lead II.

The measurements were carried out as follows: The QRS interval was measured first, from the beginning of Q to the end of S. Then the S-T interval was measured, from the end of S to the end of T. These measurements were done on three different ventricular complexes and the average of the three values obtained was taken as the duration of QRS and S-T. The Q-T interval, the duration of the electrical systole, was obtained by the addition of the QRS and the S-T intervals. For all measurements in this series, the Cambridge Record Measuring Machine was used, a comparator designed after plans of Captain B. H. Elliott, R.A.

The Q-T interval was then compared with the normal established by Fridericia. The difference between the Q-T interval of each case and that normal was calculated for each case and expressed in per

cent. Whenever possible, three electrocardiograms were taken, one before digitalization, another immediately after digitalization, and a third after digitalis had been discontinued for some time. Usually, the patients received 2.8 gm. of powdered digitalis in one week. Fig. 1 shows the electrocardiograms (Lead II only) of a typical case before and after digitalization and illustrates the method of measuring the Q-T interval.

The effect of digitalis in the *form* of the electrocardiogram has been well known since the studies by Cohn, Fraser, and Jamieson,[1] in 1915. These authors described the characteristic changes of the T-wave, gradual depression and eventual inversion, which they saw appear from thirty-six to forty-eight hours after digitalis medication was begun, and which persisted from five to twenty-two days. But they did not concern themselves with the effect of the drug on the *duration* of the ventricular complex. That effect of digitalis on the Q-T interval is presented in Table I. This shows that shortening of the Q-T interval was demonstrable in all of 21 cases. The degree of shortening varied from 2 per cent to 41 per cent. In no case was a prolongation of the Q-T interval produced. The more prolonged the Q-T interval had been before digitalization, the more marked was the shortening. In Case 16, in which a 41 per cent decrease was observed, the Q-T interval had been 23 per cent above normal before digitalization. However, patients with an electrical systole of normal duration also showed definite shortening after digitalis.

It is important to note that the shortening always took place in the S-T portion of the ventricular complex. The duration of the QRS interval was not affected by digitalis in the same way as the S-T interval. Allowing for the effect of changes in rate, it was found that only in 10 out of 21 cases was the QRS interval shortened by digitalis; in 6 cases it was lengthened, and in 5 cases it remained unchanged.

Shortening of the Q-T interval was more marked when the rate previous to digitalization was comparatively slow. In that group, the greatest degree of original prolongation was found. The degree of shortening was not proportionate to the clinical digitalis effect. The greatest shortening of the Q-T interval was not accompanied by the greatest drop in heart rate, nor by the most marked relief of symptoms of cardiac failure. Also, the shortening was not proportionate to the amount of digitalis taken.

Because the effect of digitalis on the duration of the electrical systole is so constant, it is suggested that the phenomenon may be utilized for a clinical purpose, and that measurement of the Q-T interval may serve as a new method for estimating digitalis effect.

We have been accustomed to use other methods for the estimation of digitalis effect. We observe changes in rate and rhythm, altera-

TABLE I

NO.	NAME	NO. AND DATE OF ELECTRO-CARDIO-GRAM	INTERPRETATION	RATE	QRS	S-T	Q-T	NOR-MAL DURA-TION OF Q-T	PRO-LON-GA-TION	CLINICAL DIAGNOSIS	MEDICATION	MISCEL-LANEOUS
1	T. S.	16620 8/ 9/29	Right ventricular preponderance.*	90	0.056	0.350	0.406	0.333	22%	Arteriosclerosis; cardiac enlargement; arterial hypertension; congestive heart failure.	No digitalis.	
	T. S.	16686 8/16/29	Left ventricular preponderance; notching of QRS; T-waves low; occasional ventricular premature beat.	76	0.084	0.290	0.374	0.353	6%		Tinct. digitalis, 450 minims since 8/11/29.	
2	S. P.	17001 9/19/29	Right ventricular preponderance; T_3 diphasic.	60	0.081	0.379	0.460	0.382	20%	Rheumatic mitral stenosis, mitral insufficiency, aortic stenosis and insufficiency; cardiac enlargement; congestive heart failure.	No digitalis.	Diagnosis confirmed by autopsy.
	S. P.	17069 9/26/29	Right ventricular preponderance; T_2 and T_3 inverted; P_2 and P_3 prominent; P_1 diphasic.	96	0.080	0.233	0.313	0.326	−4%		Tinct. digitalis, 400 minims since 9/19/29.	
3	A. B.	17126 10/ 2/29	Left ventricular preponderance; T_1 inverted.	78	0.087	0.358	0.445	0.350	27%	Arteriosclerosis; cardiac enlargement; arterial hypertension.	No digitalis.	Cor bovinum (x-rays)
	A. B.	17206 10/ 9/29	Left ventricular preponderance; T_1 inverted; R-T transition abnormal.	68	0.085	0.268	0.353	0.366	−4%		Pulv. digitalis, 2.6 gm. since 10/2/29.	
	A. B.	17277 10/16/29	Left ventricular preponderance; T_1 and T_2 inverted.	78	0.082	0.303	0.385	0.350	10%		No digitalis since 10/9/29.	
	A. B.	18287 1/ 8/30	Left ventricular preponderance; T_1 inverted; T_2 partially inverted.	84	0.104	0.322	0.426	0.340	25%			

*Where the term "right ventricular preponderance" is used, the ventricular complex is inverted in Lead I, upright in Lead III.

TABLE I—CONT'D

4	R. L.	17205 10/ 9/29	Slight left ventricular preponderance.	98	0.067	0.275	0.342	0.324	6%	Rheumatic mitral stenosis and insufficiency; transient hypertension	No digitalis.	Digitalis stopped because of nausea.
	R. L.	17279 10/16/29	Slight left ventricular preponderance; T_1 and T_2 lower; T_2 semi-inverted.	125	0.063	0.211	0.274	0.299	– 8%		Pulv. digitalis, 1.9 gm. 10/9/29-10/13/29.	
	R. L.	17854 12/ 4/29	Left ventricular preponderance.	104	0.060	0.269	0.329	0.317	4%		No digitalis since 10/13/29.	
5	Y. A.	17657 11/14/29	Left ventricular preponderance; T_3 inverted.	73	0.066	0.317	0.383	0.358	7%	Luetic aortic insufficiency and stenosis.	No digitalis.	
	Y. A.	17702 11/21/29	Left ventricular preponderance; T_3 inverted.	60	0.069	0.316	0.385	0.382	1%		Tinct. digitalis, 210 minims 11/15/29-11/17/29.	
6	S. S.	17620 11/13/29	Left ventricular preponderance; QRS notched in all leads; P_1 and T_1 slightly inverted.	85	0.115	0.272	0.387	0.339	14%	Arteriosclerosis; coronary arteriosclerosis; arterial hypertension; congestive heart failure.	No digitalis.	Marked dilatation of left ventricle (x-rays).
	S. S.	17727 11/21/29	Left ventricular preponderance; QRS notched in all leads; T_1 semi-inverted.	78	0.103	0.281	0.384	0.350	9%		Tinct. digitalis, 180 minims since 11/14/29.	
7	S. F.	17722 11/21/29	Tendency to left ventricular preponderance; P_3 slightly inverted.	107	0.072	0.274	0.346	0.314	10%	Rheumatic mitral stenosis	No digitalis.	
	S. F.	17782 11/27/29	Tendency to left ventricular preponderance; all T-waves flatter.	96	0.065	0.273	0.338	0.326	4%		Pulv. digitalis, 2.4 gm. since 11/21/29.	
8	G. G.	17552 11/ 7/29	Left ventricular preponderance.	80	0.058	0.290	0.348	0.346	1%	Coronary arteriosclerosis	None.	
	G. G.	17634 11/14/29	Left ventricular preponderance; one extrasystole of auricular origin recorded.	81	0.050	0.253	0.303	0.344	–13%		Pulv. digitalis, 2.8 gm. since 11/7/29.	
	G. G.	17781 11/27/29	Left ventricular preponderance; R-T transition abnormal in Leads I and II	84	0.049	0.298	0.347	0.340	2%		None since 11/14/29.	

TABLE I—CONT'D

NO.	NAME	NO. AND DATE OF ELECTRO-CARDIO-GRAM	INTERPRETATION	RATE	QRS	S-T	Q-T	NOR-MAL DURA-TION OF Q-T	PRO-LON-GA-TION	CLINICAL DIAGNOSIS	MEDICATION	MISCEL-LANEOUS
9	A. H.	17695 11/20/29	T_3 inverted.	91	0.074	0.282	0.356	0.331	8%	Transient hypertension	None.	
	A. H.	17783 11/27/29	Inversion of T and abnormal R-T transition in all leads.	70	0.074	0.263	0.337	0.362	– 7%		Pulv. digitalis, 2.8 gm. since 11/20/29.	
	A. H.	17956 12/12/29	T_3 slightly inverted.	90	0.065	0.247	0.312	0.333	– 6%		None since 11/27/29.	
	A. H.	18455 1/ 2/30	T_3 slightly inverted.	80	0.079	0.253	0.332	0.346	– 4%			
10	E. D.	16311 7/ 2/29	Right ventricular preponderance; T_2 and T_3 large; P-R, 0.28 sec.	96	0.077	0.293	0.370	0.326	13%	Rheumatic mitral stenosis and tricuspid insufficiency; Cardiac enlargement; congestive heart failure.	None.	
	E. D.	17227 10/10/29	Tendency to right ventricular preponderance; P prominent and broad in all leads; P-R, 0.28 sec.	92	0.077	0.276	0.353	0.331	7%		None.	
	E. D.	18118 12/26/29	Right ventricular preponderance; T_3 inverted; P_1 notched; P_2 and P_3 prominent; P-R, 0.34 sec.	90	0.067	0.240	0.307	0.333	– 8%		Pulv. digitalis, 3.0 gm. 12/18/29-12/26/29.	Ceased Jan. 10, 1931.
11	I. P.	18561 1/30/30	Left ventricular preponderance; T_1 slightly inverted.	87	0.069	0.239	0.308	0.337	– 9%	Arteriosclerosis; cardiac enlargement; coronary arteriosclerosis	None.	
	I. P.	18705 2/13/30	Left ventricular preponderance; T_1 inverted; T_2 lower than before.	81	0.061	0.228	0.289	0.345	–16%		Pulv. digitalis, 2.8 gm. since 1/30/30.	
12	N. K.	18854 2/26/30	Left ventricular preponderance.	89	0.080	0.320	0.400	0.334	20%	Arteriosclerosis; cardiac enlargement; coronary arteriosclerosis.	None.	
	N. K.	18954 3/ 5/30	Left ventricular preponderance; T_3 slightly inverted.	77	0.093	0.266	0.359	0.351	2%		Pulv. digitalis, 3.0 gm. since 2/26/30.	

TABLE I—CONT'D

13	I. K.	18867 2/27/30	No abnormalities.	78	0.077	0.314	0.391	0.350	12%	Arteriosclerosis; cardiac enlargement; arterial hypertension; congestive heart failure.	None.	
	I. K.	18967 3/ 6/30	Left ventricular preponderance; T_3 inverted.	100	0.075	0.268	0.343	0.321	7%		Pulv. digitalis, 2.8 gm. since 2/27/30.	
14	O. H.	16913 9/10/29	Left ventricular preponderance; T_1 slightly inverted; R-T transition slightly above base line in Leads II and III.	102	0.093	0.206	0.299	0.320	7%	Luetic aortic stenosis and insufficiency; coronary arteriosclerosis; cardiac enlargement; congestive heart failure.	None.	Diagnosis confirmed by autopsy.
	O. H.	17429 10/29/29	Left ventricular preponderance; R-T transition abnormal in Leads I and III.	83	0.105	0.250	0.355	0.342	4%		Tinct. digitalis, 300 minims.	
15	L. F.	18770 2/18/30	R_3 low; T_3 inverted.	90	0.075	0.234	0.309	0.333	– 9%	Subacute bacterial endocarditis; mitral stenosis and insufficiency; aortic insufficiency; embolic focal glomerulonephritis.	None.	Diagnosis confirmed by autopsy.
	L. F.	18806 2/20/30	T_2 and T_3 inverted.	89	0.085	0.208	0.293	0.334	–12%		Tinct. digitalis, 120 minims.	
	L. F.	18949 3/ 5/30	R_3 low; T-waves inverted in all leads; R-T transition abnormal in all leads; P_3 inverted.	76	0.080	0.187	0.267	0.352	–24%		Tinct. digitalis, 1170 minims.	
16	J. Z.	18982 3/ 7/30	T_1 inverted, cove-shaped; T_2 partially inverted; R_3 very low.	95	0.070	0.332	0.402	0.327	23%	Luetic aortitis; aneurysm; aortic insufficiency; coronary thrombosis	None.	Diagnosis confirmed by autopsy.
	J. Z.	19056 3/13/30	P-R, 0.25 sec.; occasional blocked auricular beats.	126	0.074	0.168	0.242	0.298	–18%		Tinct. digitalis, 1640 minims since 3/8/30.	
17	J. M.	20119 6/28/30	Left ventricular preponderance; T_1 semi-inverted; high voltage.	81	0.100	0.294	0.394	0.345	14%	Rheumatic aortic insufficiency; congestive heart failure.		Diagnosis confirmed by autopsy.
	J. M.	20197 7/ 9/30	Left ventricular preponderance; high voltage; T_1 and T_2 deeply inverted; nodal rhythm with P frequently following QRS.	85	0.077	0.251	0.328	0.340	– 4%		Tinct. digitalis, 240 minims 6/30/30-7/4/30.	

TABLE I—CONT'D

NO.	NAME	NO. AND DATE OF ELECTRO-CARDIO-GRAM	INTERPRETATION	RATE	QRS	S-T	Q-T	NOR-MAL DURA-TION OF Q-T	PRO-LON-GA-TION	CLINICAL DIAGNOSIS	MEDICATION	MISCEL-LANEOUS
18	S. K.	16004 6/ 1/29	Right ventricular preponderance.	100	0.113	0.244	0.357	0.321	11%	Rheumatic mitral stenosis and insufficiency; aortic insufficiency.	None.	Diagnosis confirmed by autopsy.
	S. K.	16277 6/28/29	Left ventricular preponderance.	61	0.078	0.269	0.347	0.380	– 9%		Tinct. digitalis, 795 minims since 6/1/29.	
19	I. H.	19699 5/12/30	T_2 and T_3 partially inverted; P-R, 0.24 sec.	89	0.083	0.210	0.293	0.334	–12%	Rheumatic mitral stenosis; mitral insufficiency; aortic and tricuspid insufficiency.	Pulv. digitalis, 5.4 gm. 4/14/30-5/7/30.	Diagnosis confirmed by autopsy.
	I. H.	20249 7/17/30	T continuous with QRS; P-R, 0.32 sec.	100	0.076	0.179	0.255	0.321	–21%		No digitalis 5/8/30-6/7/30; tinct. digitalis, 70 c.c. since 6/24/30.	
20	I. H.	19673 5/ 9/30	QRS notched in all leads; P_1 and P_2 notched.	78	0.079	0.312	0.391	0.350	12%	Subacute bacterial endocarditis; patent ductus; mitral stenosis and insufficiency; aortic insufficiency.	None.	Diagnosis confirmed by autopsy.
	I. H.	20042 6/17/30	Nodal rhythm; T_2 and T_3 inverted; R-T transition in Leads I and II.	91	0.065	0.207	0.272	0.331	–18%		Tinct. digitalis, 480 minims since 6/10/30.	
21	J. P.	21739 1/23/31	No abnormalities.	86	0.077	0.265	0.342	0.338	1%	Rheumatic mitral stenosis and insufficiency; aortic insufficiency.	None.	
	J. P.	21887 2/11/31	T_2 and T_3 partially inverted.	94	0.067	0.248	0.315	0.329	– 4%		Pulv. digitalis, 2.1 gm. 1/24/31-1/31/31.	

tions in the form of the T-wave, and changes in conduction time. The results of the first two of these methods were compared with those of the new method which I propose. Such comparison yielded the following results: Slowing of the rate was in evidence in only 13 out of 21 cases (62 per cent). Changes in the form of the T-wave were found in 17 out of 21 cases (81 per cent). Shortening of the Q-T interval, on the other hand, was present in all of 21 cases (100 per cent). It thus seemed proved that shortening of the Q-T interval is the most reliable criterion of digitalis effect.

Slowing of the rate is an important clinical sign of digitalis effect. But it is not a reliable indicator. The rate is always subject to many accidental influences, such as temperature, emotions *et al.* That accounts for the fact that in our series only 13 out of 21 cases showed slowing, whereas 8 showed acceleration. The changes in the form of the T-wave are better indicators of digitalis effect. They appear early, two or three hours after the administration of a single dose of the tincture equal to one minim per pound of the patient's weight (Pardee). They appear before alterations in rhythm or conduction time are evident; and they are less subject to accidental influences. In our series, 17 out of 21 cases showed T-wave changes. Here the question arises why in 4 out of 21 cases no such T-wave changes could be detected. The answer may be that T-wave changes might be so minute as to escape observation. At any rate, the results of this method depend very much upon individual interpretation and can never be expressed by actual figures.

In the same 4 cases in which no changes in the form of the T-waves were in evidence, digitalis produced definite shortening of the electrical systole varying from 7 to 36 per cent. Consequently, shortening of the Q-T interval (always related to the respective heart rates) proved a better indicator of digitalis effect on the heart than the other methods. The new method appears reliable as long as the measurements obtained are taken not at their absolute values, but in their relation to the normal values established for the respective heart rates.

The first case of the series will illustrate this point. Here, the duration of systole was 0.406 sec. before digitalization, 22 per cent above normal. The heart rate was then 90 beats per minute. Digitalis shortened the duration of systole to 0.374 second, only 6 per cent above normal, while the heart rate came down to 76. There we can say that digitalis shortened the systole by 16 per cent. But it would be incorrect simply to subtract 374 from 406 and state that digitalis shortened the systole by 0.032 second. The results of the new method cannot be expressed in seconds, but only in percentage of the normal values. Still, one definite advantage of the method remains—the digitalis effect can be expressed by a single figure.

A study of the digitalis effect on the Q-T interval necessarily leads up to the larger problem: what significance have spontaneous changes in the duration of the electrical systole? What importance, in particular, has a prolongation of the Q-T interval? Fridericia[6] reported that abnormal prolongation of systole could be produced in healthy animal hearts by overburdening them suddenly, and that in man, an abnormal increase in the duration of systole was indicative of myocardial weakness. He mentions one case of mitral stenosis in which such prolongation was the forerunner of auricular fibrillation at a time when there were no other signs indicating poor prognosis. Another author, Miki,[10] found that after a series of extrasystoles the first normal contraction may be very short; and he concluded that damage to the heart muscle was indicated by shortening of systole rather than by lengthening it. When Miki discusses clinical cases, he does not state expressly that digitalis had not been administered. The same is true of most other workers. The author's investigation bears out the fact that shortening of the electrical systole must not be attributed to myocardial damage as long as digitalis effect is not ruled out. This consideration is of great importance, because in a group of patients with cardiac failure usually very few can be found who have not received digitalis.

Pardee[17] considers it "possible that the relation between heart rate and the duration of the ventricular complex may express the degree of cardiac dilatation at the various rates." White and Mudd[18] studied the problem in 50 normal and 163 abnormal persons and came to the conclusion that "the measurement of the duration of the Q-T interval of the electrocardiogram is apparently of little or no clinical value." One factor which these authors found exerting definite influence on the duration of the Q-T interval was the content of calcium in the blood serum. Only 5 such cases were studied by them. Two cases of tetany which showed marked diminution of the serum calcium both showed prolongation of the Q-T interval beyond the normal, with a return to normal as the blood calcium rose. This relationship had already been reported by Carter and Andrus.[11]

In my own investigation, I have thought it advisable to differentiate between two types of prolongation of the electrical systole: those with a QRS interval prolonged above the normal limit of 0.09 second, and those with a QRS interval of normal duration; viz., below 0.09 second. In the first group, prolongation of the electrical systole is due to abnormal conduction. Outstanding examples of this group are cases of bundle-branch block and most extrasystoles, especially of the ventricular variety. Here prolongation of the electrical systole is brought about chiefly by the widening of the QRS complexes. I was concerned, however, only with the second group where the QRS interval is of normal duration. In those cases prolongation of the electrical systole

is brought about by lengthening of the S-T interval. It is not the spreading of the contraction, but the contraction itself that is prolonged.

I have collected 54 such cases of normal rhythm with prolongation of the electrical systole. Only patients with a Q-T interval prolonged 10 per cent or more above Fridericia's normal were included in this group so as to rule out the influence of possible errors of measurement.*

TABLE II

54 CASES WITH PROLONGATION OF THE Q-T INTERVAL
(10 Per Cent or More Above Normal.)

Arterial hypertension	24	44.4%
Rheumatic valvular heart disease	14	25.9%
Thyroid diseases*	4	7.4%
Subacute bacterial endocarditis	3	5.6%
Coronary arteriosclerosis	2	3.7%
Luetic aortic insufficiency	2	3.7%
Cerebral arteriosclerosis	1	1.9%
Cardiac neurosis	1	1.9%
Pneumonia, lobar	1	1.9%
Chronic pneumonitis	1	1.9%
Pernicious anemia	1	1.9%
Total	54	100%

*Two cases of substernal goiter with tracheal compression, two cases of Graves' disease.

All patients who had received either digitalis, which shortens systole, or quinidine, which prolongs it, were carefully excluded. Table II summarizes the diagnoses in this group. Forty-six of the 54 patients had definite evidence of heart disease; 24 out of the 54 had hypertension (44.4 per cent). The preponderance of arterial hypertension in this group is impressive. Fenn,[12] in 1922, had already found that clinical conditions accompanied by high blood pressure are often associated with prolongation of the Q-T interval. I observed that the higher degrees of prolongation occurred most frequently in hypertensive disease, and were not usually present in grave or fatal cases. Equally high values were obtained in rheumatic heart disease, although less frequently.

TABLE III

20 CASES WITH EXTREME PROLONGATION OF THE Q-T INTERVAL
(20 Per Cent to 34 Per Cent Above Normal.)

Arterial hypertension	12	60%
Rheumatic valvular heart disease	4	20%
Subacute bacterial endocarditis	1	5%
Luetic aortic insufficiency	1	5%
Graves' disease	1	5%
Chronic pneumonitis, right lung	1	5%
Total	20	100%

*The measurements in the previous series in which the effect of digitalis was studied were done twice, first without a comparator, and then again with the comparator. The results by the two methods differed so very little that it was not considered necessary to use the comparator for this and the following series.

From this group of 54 patients, there were then selected 20 patients with extreme prolongation of the electrical systole. Only those with a Q-T interval of 20 per cent or more above normal were included in this special group, which is summarized in Table III. Here 12 patients (60 per cent) had arterial hypertension as compared to 46 per cent in the larger group. All patients, except two, had very large hearts as demonstrated either by x-ray or by autopsy. Very often extreme dilatation was noted. It is certain, however, that prolongation of the electrical systole is a complex phenomenon and does not express cardiac dilatation alone. Two cases of marked dilatation were found with shortening of the electrical systole. Digitalis, which usually reduces the size of the heart but little, could not shorten the Q-T interval up to 41 per cent, if prolongation expressed dilatation only. Miki produced prolongation of the electrical systole experimentally in dogs by compressing the aorta. This experiment allows the same conclusion as does the prevalence of arterial hypertension in my group of clinical cases with prolonged Q-T interval; namely, that increased resistance to the systolic contraction of the heart is a principal factor in producing prolongation of the electrical systole.

Prolongation was found to be more frequently associated with bradycardia than with tachycardia. It would seem that with a heart rate of 60, a prolongation of 10 per cent may be of less significance than the same finding at a rate of 120. The highest degree of prolongation that I observed was 34 per cent (3 cases). It was noticed that the greatest prolongation was invariably found in those patients who showed no signs of cardiac failure. This observation, which agrees with earlier findings reported by Feil and Katz,[13, 14, 15] does not corroborate Fridericia's statement that prolongation of the electrical systole indicated myocardial weakness and poor prognosis. Rather it points toward the opposite conclusion.

TABLE IV

Q-T INTERVAL IN 14 FATAL CASES OF AORTIC INSUFFICIENCY

CASE NO.	DURATION OF R-T INTERVAL	
20339	30% prolongation	marked prolongation: 4 cases
20612	20% prolongation	
19406	28% prolongation	
15254	23% prolongation	
20119	7% prolongation	normal duration: 8 cases
18097	4% prolongation	
20476	normal duration	
16004	normal duration	
18770	normal duration	
18097	normal duration	
16913	normal duration	
18144	3% shortening	
18126	12% shortening	marked shortening: 2 cases
19024	15% shortening	
Total		14 cases

In seeking further for a possible prognostic significance of prolongation of the Q-T interval I collected a third group of cases (Table IV) made up of 14 patients with aortic insufficiency, mostly combined with other valvular lesions, who died during their hospital residence in 1930. Aortic insufficiency was selected because of its common association with extreme enlargement of the heart. Autopsies were performed on all 14 patients. Digitalized patients were carefully excluded. Only 4 of the 14 patients (29 per cent) showed marked prolongation of the electrical systole; 2 (14 per cent) showed marked shortening, and 8 (57 per cent) a normal duration of the Q-T interval. No definite prognostic significance can, therefore, be attached to either prolongation or shortening in this group.

SUMMARY

Twenty-one patients with definite cardiac disease, but with regular rhythm were selected and the effect of digitalis on the duration of the Q-T interval, the electrical systole of the heart, was studied. It was found that digitalis shortened the electrical systole up to 41 per cent in all of 21 cases. The shortening always took place in the S-T interval, while the QRS interval was neither definitely prolonged nor shortened. It is suggested that measurement of the Q-T interval may serve as a new method for estimating digitalis effect on the heart. This method was found more reliable than the older ones. Besides, it has the special advantage that it allows the digitalis effect to be expressed by a single figure.

In an effort to determine the significance of spontaneous changes in the duration of the electrical systole, especially of prolongation, 54 patients with normal rhythm and a Q-T interval prolonged 10 per cent or more above normal were collected. Twenty-four (44.4 per cent) of these 54 patients had arterial hypertension. In a narrower group of 20 patients with a Q-T interval prolonged 20 per cent or more above normal, a still higher proportion, 12 (60 per cent) had arterial hypertension. Prolongation of the electrical systole is usually associated with cardiac enlargement. That it does not indicate poor prognosis was borne out by the results in a third series, consisting of 14 fatal cases of aortic insufficiency. Only 4 (29 per cent) of these 14 cases showed marked prolongation of the Q-T interval.

I wish to express my appreciation to Dr. Marcus A. Rothschild and Dr. Irving R. Roth for their helpful suggestions.

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THE ACCURACY OF EINTHOVEN'S EQUATION*

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IN HIS earliest articles on the electrocardiogram, Einthoven[1, 2] pointed out that the three standard leads adopted by him are related in such a way that any one of them may be calculated when the other two are known. He expressed this relation in the equation:

$$\text{Lead II} - \text{Lead I} = \text{Lead III}$$

which states that the deflection in Lead II is equal to the sum of the deflections in the other two leads.

This equation has frequently led to misunderstanding. Only recently an article has been published[3] in which the statement is made that it can only be exact when the triangle formed by the three leads is strictly equilateral. Actually, the equation is based upon the simple principle that a direct measurement of the potential difference between two points will give the same result as an indirect measurement in which the potential of each point is compared with that of a third point. If the potential of the right arm is represented by V_R; the potential of the left arm, by V_L; and the potential of the left leg, by V_F; then, Lead I must be represented by $V_L - V_R$; Lead II, by $V_F - V_R$; and Lead III, by $V_F - V_L$. It is obvious that

$$(V_F - V_R) - (V_L - V_R) = (V_F - V_L) \qquad (1)$$

and consequently that Einthoven's equation must hold equally well for any kind of a triangle whatsoever.

Einthoven, Fahr, and de Waart[4] pointed out that this equation does, however, involve the assumption that the current which flows through the galvanometer has no influence upon the potentials of the extremities connected to its terminals. They state that the effect mentioned must be too small to introduce a material error because the resistance of the galvanometer and the body is very large in comparison with the resistance of the heart muscle.

In a subsequent article by Einthoven, Bergansius, and Bijtel[5] however, it is shown that the accuracy of the formula does not depend upon the resistance of the galvanometer nor upon the assumption mentioned. It is demonstrated that, contrary to an opinion still very widely held, the method of standardizing the electrocardiogram is such

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that the potential differences measured are those that would have existed had the galvanometer not been connected to the body.

Inasmuch as the proof of this important principle given by Einthoven and his associates is so brief that it is rather hard to follow and has been generally overlooked, we repeat it here in a somewhat modified form.

In Fig. 1 the electromotive force generated by the heart at any instant is represented by E_1. The right and left arms, or any two points of the body surface, are represented by R and L, respectively. Be-

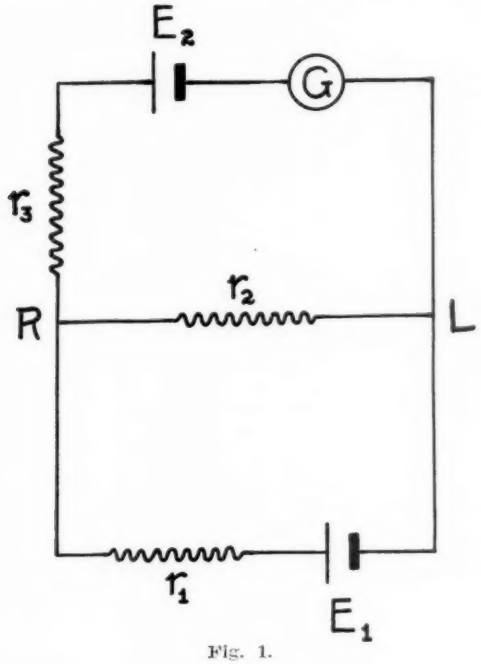

Fig. 1.

fore the attachment of the galvanometer terminals at these points the current I_1 flowing through the body circuit, which contains the resistances r_1 and r_2, is defined by the equation

$$I_1 = \frac{E_1}{r_1 + r_2} \tag{2}$$

and the potential difference between R and L by the expression

$$V_L - V_R = \frac{E_1 r_2}{r_1 + r_2} \tag{3}$$

When the galvanometer circuit containing the resistance r_3, but no electromotive force, is added by connecting the galvanometer termi-

nals at R and L, the current I_2 flowing through the main circuit; that is, through the resistance r_1, will be represented by

$$I_2 = \frac{E_1}{r_1 + \frac{r_2 r_3}{r_2 + r_3}} \tag{4}$$

and the current I_3 through the galvanometer, G, by

$$I_3 = \frac{r_2}{r_2 + r_3} \times \frac{E_1}{r_1 + \frac{r_2 r_3}{r_2 + r_3}}. \tag{5}$$

The potential difference between R and L will obviously decrease somewhat when the galvanometer is attached.

If, at some point in diastole when the electromotive force E_1, generated by the heart is no longer acting, an electromotive force, E_2 is introduced into the galvanometer circuit, the current I_4 flowing through the galvanometer will be defined by the equation

$$I_4 = \frac{E_2}{r_3 + \frac{r_1 r_2}{r_1 + r_2}} \tag{6}$$

If the value of E_2 is so adjusted that the deflection of the galvanometer in response to this electromotive force is equal to the deflection previously produced by the electromotive force generated by the heart; that is to say, so that I_4 equals I_3, then

$$\frac{E_2}{r_3 + \frac{r_1 r_2}{r_1 + r_2}} = \frac{r_2}{r_2 + r_3} \times \frac{E_1}{r_1 + \frac{r_2 r_3}{r_2 + r_3}} \tag{7}$$

or

$$E_2 = \frac{E_1 r_2}{r_1 + r_2} = V_L - V_R \tag{8}$$

Consequently, E_2 is equal to the potential difference between R and L that would have been produced by E_1, if the galvanometer had not been connected to the body circuit. In this demonstration it is assumed that the method employed to introduce the standardizing electromotive force E_2 does not alter the resistance of the galvanometer circuit. The accuracy of Einthoven's equation depends upon this requirement but upon no other condition. It is of course essential that

the electrodes used shall not polarize appreciably and that the skin be properly prepared so that it shall not introduce a leaky condenser into the circuit.

SUMMARY

The accuracy of Einthoven's equation does not depend upon the resistance of the string galvanometer. In a properly standardized electrocardiogram the deflection at any instant is an accurate measure of the potential difference that would have existed between the body points to which the galvanometer terminals were attached had the galvanometer not been connected with the body.

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THE POTENTIAL VARIATIONS PRODUCED BY THE HEART BEAT AT THE APICES OF EINTHOVEN'S TRIANGLE*

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THE electrocardiogram is a record of the time course of the difference in potential produced by the heart beat between the two points or regions of the body upon which the galvanometer electrodes rest. It may therefore be regarded as a combination of two curves, each of which represents the potential variations during the cardiac cycle beneath a single electrode. In the case of the records obtained from isolated strips of cardiac or skeletal muscle suspended in moist air, it is possible to determine the form of these constituent or unipolar curves, at least approximately, by killing the tissue beneath one electrode. Experiments of this kind have, however, no direct bearing upon the analysis of the clinical electrocardiogram. When the irritable tissue is surrounded by a large body of conducting medium, or when indirect leads are employed, it is not possible to prevent variations in the potential of one electrode by killing the tissue with which it is in contact.

For certain purposes it is desirable to know the form of the constituent curves of which the electrocardiogram is a combination, and we wish to describe a method of determining the potential variations produced by the heart beat at any point of the body. This method is based upon the principles set forth in a recent article from this laboratory.[1] It was there shown that Einthoven's equilateral triangle is based upon the laws which govern the distribution of electric currents in volume conductors. It will be recalled that Einthoven assumed that the resultant electromotive force produced by the heart at any instant may be represented by a "bipole"; that is to say, a positive and negative pole of equal strength very close together; located at the center of the triangle. The axis of this bipole, or doublet, was represented by an arrow pointing from the negative toward the positive pole; this axis is usually spoken of as the electrical axis of the heart. It was also shown, in the article referred to, that the potential V of any apex of the triangle is proportional to the cosine of the angle θ made by the electrical axis with the line drawn from the center of

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the triangle to the apex in question. Referring to Fig. 1 we may define the potentials of the three apices of the triangle as follows:

$$V_R = A \cos \theta_1 \quad (1a)$$
$$V_L = A \cos \theta_2 \quad (1b)$$
$$V_F = A \cos \theta_3 \quad (1c)$$

In these equations A is merely a proportionality factor. We need not discuss here the factors upon which its value depends since all of these remain constant under the circumstances with which we are concerned.

Einthoven represented the deflections in the three standard leads by e_1, e_2, and e_3, respectively, and expressed them in terms of the angle α (Fig. 1) and E, the manifest potential difference. If we equate the

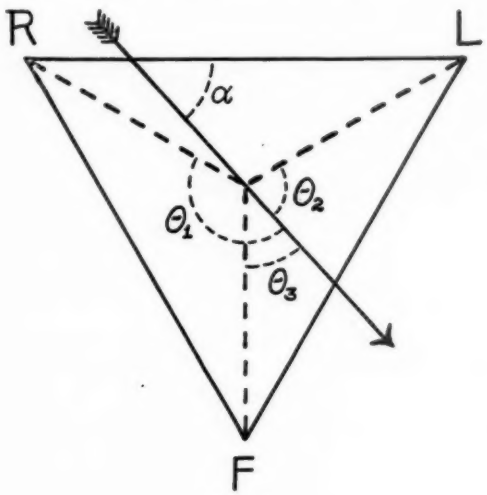

Fig. 1.

values of e_1, e_2, and e_3, given by him to those derived from the equations given above we have

$$e_1 = V_L - V_R = E \cos \alpha = A (\cos \theta_2 - \cos \theta_1) \quad (2a)$$
$$e_2 = V_F - V_R = E \cos (\alpha - 60^\circ) = A (\cos \theta_3 - \cos \theta_1) \quad (2b)$$
$$e_3 = V_F - V_L = E \cos (120 - \alpha) = A (\cos \theta_3 - \cos \theta_2) \quad (2c)$$

The angles θ_1, θ_2, and θ_3 may, however, be expressed in terms of α; viz., $\theta_1 = 210^\circ - \alpha$; $\theta_2 = \alpha + 30^\circ$; $\theta_3 = 90^\circ - \alpha$. By substituting these values in the first of the equations (2a) just given, we obtain

$$e_1 = E \cos \alpha = A [\cos (30^\circ + \alpha) - \cos (210^\circ - \alpha)] \quad (3)$$
$$= A (\sqrt{3} \cos \alpha)$$

Consequently,

$$E = \sqrt{3} A$$
$$V_F = \frac{E}{\sqrt{3}} \cos (90^\circ - \alpha) = \frac{E}{\sqrt{3}} \sin \alpha. \quad (4)$$

We now have an expression for the potential of the left leg in terms of E and α. We may obtain a more convenient expression in the following way:

$$e_2 + e_3 = E\ [\cos\ (\alpha - 60°) + \cos\ (120° - \alpha)] \qquad (5)$$
$$= E\ (\sqrt{3}\ \sin\ \alpha).$$

Consequently,

$$V_F = \frac{e_2 + e_3}{3} = \frac{E}{\sqrt{3}}\ \sin\ \alpha. \qquad (6a)$$

In the same way it may be shown that

$$V_R = -\ \frac{e_1 + e_2}{3} \qquad (6b)$$

$$V_L = \frac{e_1 - e_3}{3} \qquad (6c)$$

These expressions give the potentials of the three extremities, or the three apices of Einthoven's triangle, in terms of the deflections in the three leads. They therefore enable us to determine the potential at any point of the body at any instant with reference to the potential of this point at a time when the heart is producing no electric currents, a potential which we may for our purposes regard as zero. In other words, we can determine the potential variations produced by the heart beat at any body point. To do so we need merely to place the right-hand electrode of the galvanometer at this point and the left-hand electrode upon one of the extremities. The resulting record will give the difference in potential between the point under investigation and the extremity employed. The potential of the former is then computed by subtracting from the recorded curve the potential variations of the latter determined by formula from the appropriate standard leads. In order to carry out this procedure properly, two galvanometers are required. First of all, the three standard leads are recorded, taking two leads simultaneously so that synchronous points may be identified. The right-hand electrode of one galvanometer is then placed in contact with the point under investigation and the left-hand electrode upon the left leg. A record is then made, the second galvanometer being employed to inscribe Lead I simultaneously.

We may represent the potential of the point chosen by V_P and the deflection at any instant in the lead from this point to the left leg by e_4. We then have

$$V_F - V_P = e_4 \qquad (7)$$

$$-\ V_P = e_4 - \frac{e_2 + e_3}{3} \qquad (8)$$

In order to avoid confusion some explanation of the plus and minus signs in these and preceding equations is necessary. It has become conventional to take electrocardiograms in such a way that relative

negativity of the electrode attached to the right hand in Leads I and II produces an upward deflection in the completed record. Since an upward deflection is considered positive in measuring the electrocardiogram, it is necessary to represent Lead I by $V_L - V_R = e_1$ in order to indicate that e_1 becomes more positive as the right arm becomes more negative or the left arm more positive. In other words, the derivative of e_1, with respect to V_R must be negative and its derivative with respect to V_L, positive. The signs in the corresponding formulas for the other standard leads are determined in the same way. It has also become conventional in leading from points on or near the heart to points at a distance to use the right-hand electrode as the exploring electrode, so that an upward deflection indicates relative negativity of the point under investigation. For this reason negative values of V_P in equation (8) are plotted above the base line and positive values below. In plotting V_F, the potential of the left leg, which is ordinarily attached to the left-hand electrode in taking both standard and special leads, positive values are plotted above the base line and negative values below, because variations in the potential of the left-hand electrode have an effect upon the electrocardiogram opposite in sign to that produced by variations in the potential of the right-hand electrode.

In the article from this laboratory to which we have already referred it was pointed out that when one electrode is placed very close to the heart or upon its surface, the position of the second electrode, so long as it is distant from the heart, is of very little importance. The reason lies in the character of the laws which govern the distribution of electric currents in volume conductors. The magnitude of the effect exerted by the position of the distant electrode may now be accurately determined. Suppose that the right-hand electrode is placed upon the exposed ventricular surface and the left-hand electrode upon the left leg. In such direct leads the galvanometer may be employed at one-twentieth of its normal sensitivity. In order to free a curve obtained in this way from the influence exerted by potential variations at the leg electrode, it is only necessary to subtract from each ordinate $\frac{e_2 + e_3}{60}$ millimeters, where e_2 and e_3 represent the deflections in Leads II and III, respectively, at the corresponding instant in the cardiac cycle. It is obvious that curves of this kind are, for all practical purposes, records of the potential variations of the exploring electrode alone.

In precordial leads, in which the exploring electrode is placed upon the precordium and the indifferent electrode upon the left leg, the galvanometer is ordinarily employed in this laboratory at one-half its normal sensitivity. To free curves obtained in this way from the influence exerted by potential variations at the distant electrode it is necessary, therefore, to subtract from each ordinate $\frac{e_2 + e_3}{6}$ millimeters.

The potential variations of the leg electrode have a much greater influence upon the form of these curves than upon those obtained by direct leads of the kind mentioned. It is hoped that a method of estimating the magnitude of this influence and of eliminating it when desirable will be of service in their interpretation.

SUMMARY

A method is described by means of which it is possible to determine the potential variations produced by the heart beat at any one or all of the apices of Einthoven's equilateral triangle.

It is consequently possible to determine the potential variations produced by the heart beat at any point of the body by leading from this point to the left leg, or the left or right arm, and subtracting the effect produced by the potential variations of this extremity from the recorded curve.

It is possible by this method to free curves obtained by leading from points on or near the heart to points at a distance from it, such as points on the left leg, from the influence exerted by potential variations at the distant electrode.

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A REPORT OF TWO CASES OF LOCALIZED PLEURAL EFFUSION IN HEART FAILURE*

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INTRODUCTION

THE first report of localized pleural effusion during the course of heart failure appeared two years ago. This patient, reported by Stewart,[1] developed interlobar pleural fluid during each of four attacks of heart failure. The effusion disappeared with each recovery and its site was found at autopsy. Kiser[2] later reported a similar case in which the lesion was, however, not verified by autopsy. The present report deals with two additional cases, in one of which the existence of the process is confirmed by necropsy.

Search of the literature failed to bring to light any evidence that such a phenomenon had been noted before Stewart's report. Von Jürgensen[3] has made the statement that obliteration of the pleural cavity on one side altered the usual course of bilateral effusion in so far as it limited it to the other side. Upensky,[4] in a report of 16 cases of localized tuberculous pleural effusion, included one, Case No. 15, which from the x-ray photographs alone might have been regarded as due to effusion resulting from heart disease. In the first x-ray photograph the image of a large heart was seen and the shadow of an interlobar effusion. The second, taken after eight months, showed that the fluid had disappeared. The heart appeared much smaller, but since the history is insufficient and since there is lack of data concerning the x-ray technic, it is impossible to judge whether or not the effusion was due to cardiac failure. Freedman[5] in an article on the diagnosis by x-rays of encapsulated effusions appends, to his formal list of causes of encapsulated fluid, all of which were infectious in nature, cardiac failure. He notes, however, that this condition is rare. It seems desirable therefore to report two additional cases exhibiting this phenomenon.

REPORT OF CASES

Case 1.†—F. K., Hospital No. 7464, a white male carpenter aged about seventy years, complained of swelling of the feet and shortness of breath. The family history was unimportant. He had always enjoyed general good health. Frequent attacks of tonsillitis early in life led to the removal of his tonsils. Seven years

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†We are indebted to Dr. Clarence de la Chapelle for referring this case to us from the Third New York University Medical Division, Bellevue Hospital, New York.

before admission (July 24, 1930) he had suffered from a febrile illness termed "double pneumonia." An inguinal hernia had been present for seven years.

In May, 1930, while still working regularly, he noticed shortness of breath and swelling of the ankles. Both increased rapidly in severity until he entered Bellevue Hospital where, without medication, edema disappeared during two weeks' rest in bed. On July 24, 1930, he was transferred to this hospital.

The patient was an emaciated elderly white man, senile, and deaf. His temperature was 100° F. His body weight was 72.2 kilograms. He was slightly dyspneic. There was slight cyanosis of the lips and finger nail beds. The general stigmata of arteriosclerosis were present. The peripheral vessels were tortuous and thickened and there was in both eyes a well-marked arcus senilis. The skin was clear, quite loose, and dry. A sebaceous cyst of the scalp was present.

The head was normal in contour. The hearing was markedly diminished, but the ear drums, though thickened, were intact. The pupils were small, round, equal, and regular; they reacted neither to light nor in accommodation. No obstruction of the nose was present. The septum was intact. Many teeth were carious. The tongue was clean and was protruded readily in the midline. The pharynx was negative. The tonsils were large but not injected. The jugular veins were moderately distended. No episternal pulsation or tracheal tug could be felt. The lymph nodes were enlarged. The respiratory excursions were somewhat limited on both sides. The lungs were clear on percussion. The breath sounds were vesicular but a moderate number of moist râles were present at the bases of both lungs posteriorly. The rate of breathing was 32. Over the precordium no pulsations, no thrills nor shocks were felt. The area of relative cardiac dullness was increased, extending 11.5 cm. to the left of the midline in the fifth intercostal space, and 6 cm. to the right in the fourth. The heart sounds were faint but clear. No murmurs were heard.

In an x-ray photograph taken on July 24, 1930, the lung fields were relatively clear (Fig. 1-*A*). Areas of mottled cloudiness at the bases, more marked on the right side, were present. The root shadows were increased in size. Extending outward and upward from the right hilus to the lateral chest wall at the level of the third rib was a semi-elliptical shadow with a well-defined border, the straight margin of which faced upward. It suggested the presence of fluid encapsulated in the fissure between the upper and middle lobes. The right costophrenic angle was obliterated and the diaphragmatic line was flattened probably due to a small accumulation of fluid or to old adhesive pleurisy. The heart was markedly enlarged, measuring 20 cm. in the transverse diameter—12 to the left, 8 to the right. The width of the chest was 29 cm. The aortic arch was prominent; a well-marked calcified plaque was visible.

The rhythm of the heart was totally irregular and the radial pulse was irregular in both time and force. The rate, counted at the apex was 120, and at the radial artery 104 per minute, resulting in a pulse deficit of 16 beats per minute. The electrocardiogram showed that auricular fibrillation was present and that occasional ventricular premature contractions took place. The systolic blood pressure measured approximately 140 mm. Hg., and the diastolic, 100. The liver was enlarged, extending 5 cm. below the costal margin in the right midclavicular line. It was firm but not tender. The kidneys and spleen were not felt. A large, easily reducible right inguinal hernia was present. The external genitalia were otherwise normal. A small amount of soft edema was present over the shins. There was no clubbing of the fingers and toes. The tendon reflexes were active and equal on the two sides. No patellar or ankle clonus could be evoked. The Babinski test elicited ventral flexion on both sides.

The examination of the urine was negative except for the presence of a very faint trace of albumin. The urinary sediment consisted of deposits of amorphous urates. The Wassermann reaction of the blood was negative.

The diagnosis was general arteriosclerosis, chronic myocarditis, cardiac hypertrophy, auricular fibrillation, congestive heart failure, and interlobar pleural effusion.

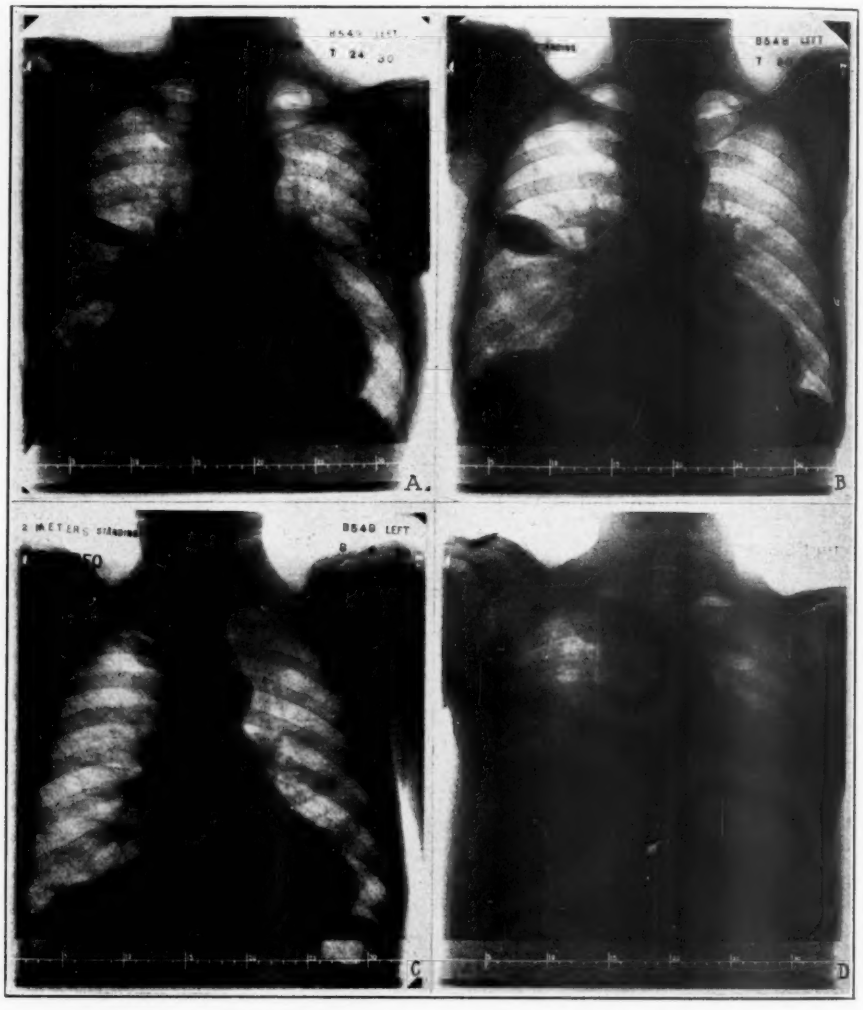

Fig. 1.—Case I. A. X-ray photograph on admission showing size of interlobar effusion when first seen. B. Six days later—effusion increased with increase in signs of heart failure. C. Showing disappearance of the interlobar fluid six days after administration of digitan. D. Post-mortem x-ray picture showing reaccumulated interlobar fluid.

During the first four days in the hospital the condition of the patient grew gradually worse. The cardiac rate increased from 120 to 140 per minute and the pulse deficit from 16 to 36 per minute. The rectal temperature rose by steps from 100.4° to 103.6° F. Although there was a loss of 4 kilograms in body weight

during this period, the urinary output continued low and the amount of edema remained unchanged. Digitan, 1.0 gm. (Merck), was administered within twenty-four hours. The following day (July 30) a second x-ray plate of the chest was made (Fig. 1-*B*) and showed that the shadow suggesting interlobar pleural effusion had doubled in size, being now ovoid, the upper border as well as the lower being convex. Forty-eight hours after the administration of digitalis, the cardiac rate had fallen to 90, the pulse deficit was only 10 per minute, and the temperature was normal. There was moderate diuresis and six days later (August 4) the patient's body weight had decreased 8 kilograms more. At this time a third x-ray plate (Fig. 1-*C*) was taken. The shadow had disappeared, leaving only a thin line to mark the site.

From this time until discharge on September 5, one month later, the patient steadily improved, and the temperature remained normal. There was no evidence of heart failure other than slight edema of the ankles which always disappeared by morning. X-ray photographs taken weekly showed that the shadow which had been present in the right upper chest remained absent.

Not quite four weeks after discharge the patient returned (September 30) for examination in a severe attack of heart failure. Extreme dyspnea, intense cyanosis, and anasarca of the lower half of the body were present. Death occurred before he could be examined. An x-ray plate of the chest taken post mortem demonstrated the return of the shadow between the upper and middle lobes of the right lung (Fig. 1-*D*). It was much larger than during the former attack of failure and was roughly proportional to the greater amount of edema.

The changes in size of the area of the heart in this series of films are interesting. In Fig. 1-*A* it measures 234.5 sq. cm., the transverse diameter being 20.5 cm. In Fig. 1-*B*, taken twenty-four hours after completion of the administration of digitalis, it measures 175.5 sq. cm., the transverse diameter being 20 cm. This represents a decrease of 25 per cent from the original size. In Fig. 1-*C* it measures 17.5 cm. in the transverse diameter and 163 sq. cm. in area. It is noteworthy that the decrease in size had taken place almost entirely in the right side of the heart. The haziness of Fig. 1-*D*, taken post mortem, makes accurate measurement impossible. The conditions under which it was taken make it, furthermore, incomparable with the other photographs. It is obvious, however, that the heart shadow is much greater than in Fig. 1-*C*.

Summary of Post-mortem Examination (Dr. C. P. Rhoads). The complete anatomical and microscopical diagnosis post mortem is given and a detailed description, pertinent to the subject of this report only, of the heart and lungs.

The left thoracic cavity contained 475 c.c. of rather thick, straw-colored fluid which clotted on standing. The pleural surfaces were smooth and glistening, without adhesions. The right pleural cavity was completely obliterated, the visceral and parietal pleurae being firmly adherent due to dense, fibrous adhesions. The right lung was removed together with the visceral and parietal pleurae. It failed to collapse. When a small incision was made about 4 cm. to the right of the midline, it entered, just under the surface, an opening between the upper and middle lobes, about 1 cm. in diameter, which led to a large oval cavity (Fig. 2), containing about 250 c.c. of straw-colored fluid of medium consistency which clotted on standing. This cavity measured 12 cm. in the greatest diameter horizontally and 8 cm. in the greatest diameter vertically. The cavity was lined with thick, somewhat trabeculated, grayish, ragged, fibrous tissue. The surface of the entire lung could not be separated from the adherent pleurae. A mass of fine to medium coarse, ragged, fibrous adhesions, gray to gray-white in color, covered the lungs, through which the lung parenchyma, blue-gray with black markings, could

be seen. The left lung collapsed partially. The surface was gray-blue, mottled with purple, and showed normal black tracings. The surface on cut section showed a fairly uniform red to red-purple color and exuded a moderate amount of thin, bloody fluid. The bronchi contained a moderate amount of mucus, somewhat blood-tinged. The vessels showed no abnormalities. The surface of the pericardium was smooth and glistening and the cavity contained about 75 c.c. of rather thin, yellowish fluid which clotted on standing. The epicardium anteriorly presented a thickened, somewhat elevated, grayish-white patch of fibrous tissue measuring roughly 8 cm. in diameter. The heart was dilated, extending 15 cm. to the left of the midline and 4 cm. to the right. The color was pale reddish-brown. The consistency was soft. The myocardium was light brown. Five depressed, oval, gray

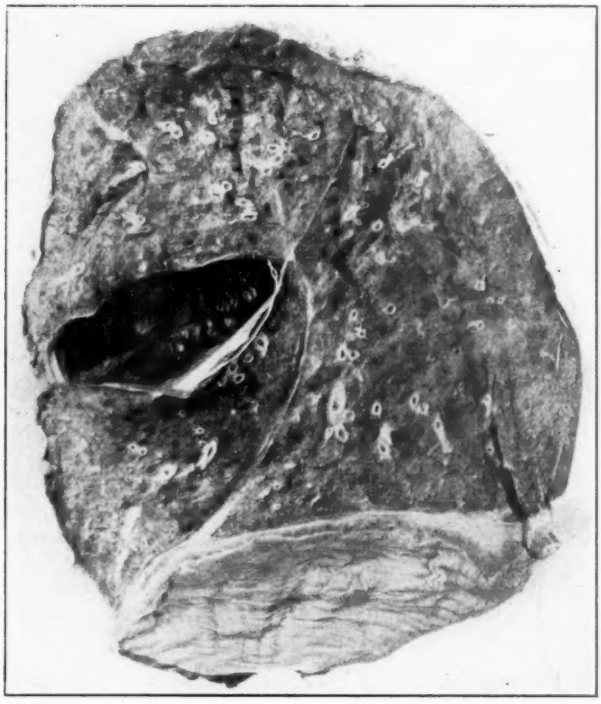

Fig. 2.—Photograph of sectioned lung (Case I). The thickened parietal pleura is well shown. Note normal pleura at site of cavity.

to gray-white areas of scar formation were present on the anterior surface of the left ventricle, from 0.5 to 1 cm. in diameter. They extended a similar distance into the ventricular musculature. At the apex there were scattered grayish areas of fibrosis of small size and indefinite outline. The myocardium of the right ventricle ranged from 0.2 to 0.3 cm., whereas that of the left ventricle ranged from 1 to 1.5 cm. in thickness. The endocardium presented no abnormalities except a few yellowish flecks 2 to 3 mm. in diameter around the base of the mitral valve. The chordae tendineae and the papillary muscles also presented no abnormalities. The tricuspid valve measured in circumference 12 cm.; the pulmonary valve, 9 cm.; the mitral valve, 10.2 cm.; and the aortic valve, 8.2 cm. The coronary arteries presented a very marked degree of atheromatous change, as evidenced by a large number of discrete and coalescent, raised, rather smooth, soft to firm, irregular

yellow to yellow-white plaques, most marked near the aorta and decreasing in frequency as the apex of the heart was approached, although very little of the intimal surface was spared. Ulceration was rare.

The aorta also presented a very marked degree of atheromatous change which was most marked at the arch, sparing the tissue near the aortic valve almost completely. The arch and the thoracic and abdominal portions of the aorta presented an enormous number of roughly circular or oval, raised, smooth, soft to very firm, yellow to yellowish-white areas. Those in the arch were extremely hard and inflexible, whereas the degree of calcification became less as one proceeded caudally. At about the level of the twelfth thoracic vertebra the intima of the aorta was ulcerated, the base of the ulcer presenting a depressed ragged surface 0.5 cm. in diameter which communicated with the adventitia. Superficial ulcerations were present elsewhere, showing a granular, reddish, hard base, surrounded by raised, smooth, thickened aortic intima.

On microscopical examination, the lungs presented no abnormality. In the heart there was extensive replacement of the myocardium by connective tissue. In the aorta there were subintimal collections of lipoid and cholesterin crystals. There was intimal proliferation. At one point there was an ulcerated necrotic plaque, the intima of which was thickened and had ruptured. There was infiltration with lipoid material. The vasa vasorum presented marked inflammatory changes. Besides these changes, there were the usual cholesterin subintimal infiltrations and intimal thickenings. At other portions there were typical atheromatous plaques with calcification together with marked perivascular infiltration in the adventitia. The coronary arteries exhibited very marked infiltration with cholesterin crystals and vacuolated cells. The vasa vasorum showed perivascular infiltration. The aortic and mitral valves presented no abnormalities.

Examination of the fluid obtained from the oval pleural cavity was as follows: sp. gr. 1.010, albumin 0.9 gm. per liter, leucocytes, 32 cells per c.c. On cultivation there was isolated a hay bacillus. This fluid was identical with that found free in the left pleural cavity.

As in Stewart's case, the whole right pleural cavity was obliterated, the pleura lining the sac of fluid being the only relatively normal pleura left. There were no areas of inflammation in the lungs; the negative cultures, the low specific gravity, and albumin content of the fluid showed that it was a transudate. The fluid was undoubtedly the result of cardiac failure.

Case 2.—E. K., Hospital No. 4464, was a man fifty-seven years of age. He was always a vigorous active person in good health. No attacks of tonsillitis, rheumatic fever, or chorea were recalled. He suffered from three Neisserian infections as a young man, but no history of syphilis was obtained. His wife and two children were living and well.

In the spring of 1920, two years prior to the first admission, he experienced dyspnea on rapid walking and on climbing stairs. Three months later swelling of the ankles appeared in the evening. A physician then prescribed digitalis and improvement followed. Except for an occasional rest of two or three days a month he continued to work as formerly. Edema and dyspnea remained approximately at the same degree for a year. In November, 1921, dyspnea and edema began to increase in severity until three months later dyspnea was severe even at rest and edema extended to the thighs. In January, 1922, the abdomen began to enlarge.

He had not experienced palpitation, precordial pain, or cough. Cyanosis had not been observed. Bleeding from hemorrhoids had been present for two years, since the onset of the illness.

On February 2, 1922, at the time of admission to the hospital the state of nutrition and muscular development were good. Moderate orthopnea and slight dyspnea were present. The temperature was 100.4° F. (rectal). The skin was

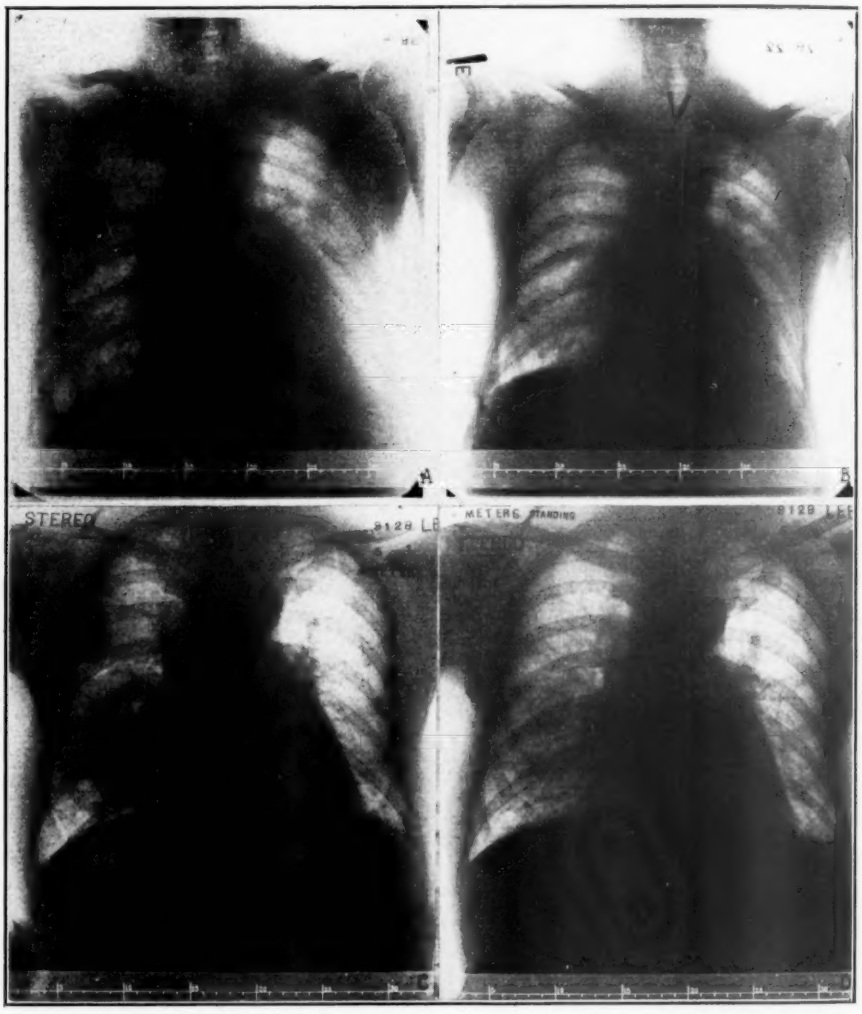

Fig. 3.—Case II. A. X-ray photograph showing effusion over the right upper lobe occurring during first attack of heart failure. B. Twenty-five days later—interlobar fluid disappeared. C. Eight years later during second attack of heart failure showing a precisely similar effusion. D. Five days after C following recovery from second attack of heart failure.

pale. The lips, ears, and finger tips were faintly cyanotic. The examination of the ears was negative. The teeth had been much treated; pyorrhea alveolaris was present. The tonsils were not enlarged. The nasal septum was intact. The extra-ocular movements were well performed. The pupils were round, equal and regular, and reacted normally to light and in accommodation. The jugular veins were

somewhat distended. There was no enlargement of the thyroid or of the superficial lymph glands. A tracheal tug was not present. The right half of the chest was flattened when compared with the left and the respiratory movements were somewhat limited. Scoliosis of the vertebral column in the thorax, convexity being to the left, was present, and was well exhibited in an x-ray photograph taken on February 3, 1922. Percussion demonstrated marked dullness below the angle of the scapula on the right side posteriorly; in this region, vocal fremitus and the breath sounds also were diminished. Crackling râles were heard at both bases. There was no area of paravertebral dullness. On palpation, localized pulsation at the base of the heart and a systolic shock at the apex were felt. The relative cardiac dullness extended 11 cm. to the left of the midline in the fifth intercostal space and 4.5 cm. to the right in the fourth. The pulse rate was 90; the respirations were 24 per minute. The systolic blood pressure measured 124 mm. Hg., the diastolic, 68. Owing to the presence of scoliosis and the consequent deformity of the chest, the shape of the heart was distorted. It seemed to be enlarged, but exact measurement was impossible. The rhythm was totally irregular as demonstrated in electrocardiograms. The sounds were vigorous and especially so were the first sound at the apex and the second sound over the pulmonic area. A protodiastolic gallop was heard over the whole precordium. No murmurs were heard. The root shadows were of increased density and the outline of the diaphragm was hazy. Of particular interest was a zone of increased density 1.5 cm. in diameter surrounding the upper lobe and lying against the lateral chest wall (Fig. 3-*A*). There was a convex widening of this shadow at the level of the third intercostal space anteriorly, bulging inward for 2.5 cm. at a point where one might expect the lateral end of the interlobar fissure between the upper and middle lobes to be. The shadow suggested encapsulated fluid or a markedly thickened pleura. The radial pulse was irregular and quick. The peripheral arteries were palpable but not markedly thickened. The abdominal cavity was distended with fluid; the liver edge was felt at a level of 2 cm. below the costal margin in the mammillary line. The spleen was easily palpable. General anasarca of the lower half of the body was present. There were numerous varicose veins in the calves of the legs.

The specific gravity of the urine varied between 1.027 and 1.013. The tests for sugar were negative. Albumin, present in moderate amounts on admission, disappeared by the end of the third week. Red and white blood cells were no longer observed at the end of the third week after admission to the hospital. The urea nitrogen in the blood measured 59 gm. per liter. The phenolsulphonephthalein excretion in two hours was 42 per cent.

The count of the red blood cells was 4,500,000 and of the white blood cells 12,800 per cubic mm. A test for the oxygen capacity of the blood showed that there was 6.85 gm. of hemoglobin per 100 c.c. In a differential count the polymorphonuclear neutrophiles were 77 per cent; polymorphonuclear eosinophiles 2 per cent; polymorphonuclear basophiles 1 per cent; monocytes and lymphocytes 20 per cent. The reaction of the blood serum on February 11 to the Wassermann test in cholesterin antigen was ++ and ± in alcoholic antigen with ice box fixation; on March 23, in cholesterin antigen it was ++++ and +++ in alcoholic antigen; on April 28 in cholesterin antigen with ice box fixation, it was ++++ and negative in alcoholic antigen.

During the first three days in the hospital (February 2 to February 5) the temperature rose from 100.6° to 104° (rectal). A cough developed and mucopurulent sputum tinged with blood was expectorated from which was cultured a Type IV Pneumococcus. The cardiac and radial pulse rates rose from 106 and 96

to 140 and 104, respectively. On the fourth and fifth days (February 6 and February 7) digitan, 1.2 gm. (Merck), was given within thirty-six hours. Subsequently the patient was kept under the influence of digitalis by the administration of small doses. Although the cardiac rate was slowed by digitalis, there resulted very little increase in the urinary output, slight loss of weight, and no disappearance of edema. The use of theocin was also without diuretic effect. Thoracentesis was performed on two occasions. A very resistant pleura was encountered but fluid was not obtained. The temperature fell slowly to 101°.

On February 13, the rhythm of the heart abruptly became normal. Two days later, after 0.5 gm. more of digitan had been given, excellent diuresis occurred. At this time the x-ray photograph was identical with the one taken on admission (Fig. 3-A). During the next ten days (to February 23) the body weight fell from 72.8 to 65.2 kg. and edema, ascites, and breathlessness disappeared. A few moist râles were still heard at the bases of the lungs. An x-ray photograph taken on February 21 showed that the shadow about the upper lobe had diminished to one-half its width, while in one taken on February 28 (Fig. 3-B) it had completely disappeared.

Until April 28, 1922, he remained in a state of cardiac compensation, the heart rhythm being regular. Potassium iodide and mercuric inunctions were given. Those teeth showing abscesses at the roots were extracted. When he was discharged, a moderately enlarged liver and spleen were the only apparent residua of his attack of heart failure. An x-ray photograph taken on discharge showed that the shadow at the periphery of the right upper lobe had not returned.

He was examined at bi-monthly intervals until February of 1924. During 1923 the rhythm of the heart reverted to that of auricular fibrillation but with the administration of digitan (Merck), adequate compensation was maintained. Although the liver remained large and slight pitting edema of the ankles was sometimes present, he continued at active work. He was not examined during the next four years, but in 1928 returned, stating that he had been quite well during the whole interim. The rhythm of the heart was again normal. X-ray photographs taken during the period of six years had not shown a return of the shadow about the right lobe.

He disappeared again for two years, but on April 23, 1930, eight years after the first attack of heart failure, and ten years after the onset of the first symptoms, he returned to the hospital suffering from a moderately severe attack and was admitted for the second time.

He had worked steadily until two weeks before when dyspnea reappeared. Slight pitting edema, which had been present off and on for eight years, slowly increased. The abdomen had also enlarged, and he became aware of a sense of oppression in the epigastrium.

The physical examination and, indeed, the course of his illness were so extraordinarily similar to those of his first admission, except that the attack was not so severe, that a detailed description of them is unnecessary. Only relevant phenomena or significant differences from those present formerly need be mentioned.

The general physical examination remained unchanged. The bases of the lungs were fixed. Râles were heard at both. The size of the heart was approximately as before; the sounds were clear, the rhythm was totally irregular and an electrocardiogram confirmed the fact that auricular fibrillation was present. No murmurs were heard. The liver and spleen were enlarged; ascites was present. Edema was much less marked, extending only to the knees.

The Wassermann reaction of the blood was still positive but only when cholesterinized antigen was used. The count of the white blood cells was not increased.

In general the x-ray photograph resembled those made during his visits to the clinic. In addition, adhesions at the bases were present and a well-defined opacity in the left lower lobe was noted. The shadow surrounding the right upper lobe noted during his first failure (Fig. 3-A) was absent.

Fluid was not obtained on thoracentesis on April 28. In an x-ray photograph taken on May 1, the shadow at the right base persisted. At the periphery of the right upper lobe an opaque shadow bulging into the region of the interlobar fissure now appeared, identical in outline with that seen eight years before (Fig. 3-C). On May 3, fever of 100.4° F. occurred, increasing the following day to 101.8°, accompanied by cough and expectoration of bloody sputum. No change, however, was observed on examination of the chest. By May 7, the temperature had entirely subsided, the cough had improved, edema and dyspnea had decreased. An x-ray photograph taken on May 6, the last day of fever (Fig. 3-D), showed that the shadow about the right upper lobe had also disappeared. When the patient was discharged on June 14, an enlarged liver and spleen were the only signs remaining of heart failure. He remains well and at work.

SUMMARY AND CONCLUSIONS

Two cases in addition to those already reported are described in this report in which, with recurrent attacks of heart failure, localized opaque areas in x-ray plates in the right upper half of the thoracic cavity appeared before improvement of the signs of heart failure began, and disappeared with the disappearance of edema and general recovery. In both cases similar shadows reappeared with the second attack. One of the patients died during the second attack. In this case, autopsy showed that the whole right pleural cavity, with the exception of the small portion between the right upper and middle lobes which constituted the site of effusion, was obliterated. Enclosed between these surfaces of normal pleura about 250 c.c. of fluid, having all the characteristics of a transudate, were found.

In all the cases, including the two previously reported, it is noteworthy that the encapsulated pleural effusion occurred during the first attack, and that the pleura was thickened on the side of the effusion in three of the four. In two, at autopsy, the whole pleural cavity was obliterated save in the region of the effusion. In the third, that the pleura was thickened was demonstrated by the difficulty of performing thoracentesis. Only one case gave a history of previous pulmonary infection.

It seems likely therefore that the occurrence of localized pleural effusions like these is dependent on the existence of extensive adhesive pleurisy antecedent to the development of heart failure.

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THE INCIDENCE OF HEART DISEASE AND OF THE ETIOLOGICAL TYPES IN A SOUTHERN DISPENSARY*

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GALVESTON, TEXAS

IN VIEW of the prominence that organic heart disease has assumed as a cause of death in the United States in the past few decades, the prevention of cardiovascular diseases has become one of the outstanding problems of preventive medicine. Material accomplishments in the direction of the prevention of heart disease cannot be anticipated until the etiological factors are clearly defined and the accessory elements of predisposition recognized. For that reason any contribution to our present knowledge of the causal agencies of heart disease is at this time most desirable. Important additions to our information on the subject have been made by recently reported statistical studies on the incidence of heart disease and of the various etiological types in different sections of the United States. With the successive appearance in the literature of reports of such statistical studies from widely separated sections of the country, it becomes more and more obvious that such factors as climate, geographical location, race, economic status, and social strata exert a profound influence on the unknown causal agents of heart disease in general and the various etiological types in particular.

Among the contributions to the statistical data on the incidence of heart disease and of the etiological types is the report of Stone and Vanzant,[1] who in 1927 reported an analysis of 915 cases of organic heart disease seen in all Services of the John Sealy Hospital of Galveston over a period of seven years. The value of this study is enhanced by the fact that it included private as well as charity patients, two entirely different social strata therefore being represented. However, whether or not this report gives a fair index of the incidence of the various etiological types of heart disease in this community is open to question for the reasons that follow. First, the majority of patients with heart disease do not enter the charity wards until they are in dire need of hospitalization. Thus it is apparent that many patients with heart disease are not included in a study confined to hospital cases. Also, as will be pointed out later, certain etiological types of heart disease produce greater disability than other types and consequently under the circumstances will receive an unfair representation in the hospital wards. Second, because of the limited facilities for negro charity patients as compared

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with white patients in the John Sealy Hospital, an accurate incidence study of the community population is impossible for, from what is to follow, it is evident that organic heart disease is much more prevalent in the negro than in the white race. The truth of the statement by White and Jones[2] that "no single series of patients—private, hospital, or clinic—gives a correct incidence of heart disease" should be reiterated.

MATERIAL STUDIED

In the seven and one-half year interval dating from January 1, 1924 to July 15, 1931, 49,880 new patients were seen in all Divisions of the Out-Patient Department of the John Sealy Hospital. Of this number 10,188, or 20.4 per cent, came under observation in the Medical Division. This latter group was composed of 4,252 (41.7 per cent) white persons of whom 2,570 were males and 1,682 females; and 5,936 (58.3 per cent) negroes of which 3,188 were males and 2,748 females. Of the 10,188 patients seen in the Medical Division 1,660 were found to have organic heart disease. These 1,660 cases of heart disease constitute the basis for this study and include only those patients who presented definite evidence of organic heart disease as determined by the history and physical examination, and confirmed by the Wassermann reaction, teleroentgenogram, electrocardiogram, and renal function tests when indicated. Those cases in which the diagnosis of heart disease remained questionable, after special diagnostic measures had been resorted to, are not included in this study.

This group of 1,660 patients with organic heart disease with reference to race was composed of 1,172 (70.6 per cent) negroes and 488 (29.4 per cent) white patients; with reference to sex, 719 (43.2 per cent) females and 941 (56.8 per cent) males; and with reference to both race and sex, white females 11.3 per cent, white males 18.1 per cent, negro females 32 per cent, and negro males 38.6 per cent.

CRITERIA EMPLOYED FOR ETIOLOGICAL CLASSIFICATION

In cataloguing the cases of heart disease according to etiology, as simple a classification as possible was employed. Multiple etiological factors were present in a number of instances, and under such circumstances the final grouping of the case was dependent upon what causative factor was considered to be the primary condition. The criteria for the diagnosis of the etiological types of heart disease as proposed by the Heart Committee of the New York Tuberculosis and Health Association[3] were used, with the modifications indicated below.

Hypertensive Heart Disease.—Included in this category are those cases which presented a persistent elevation of both the systolic and diastolic blood pressures (above 150 mm. Hg. systolic and 95 mm. Hg. diastolic) associated with demonstrable enlargement of the heart either

without impairment of renal function or with evidence that such impairment was secondary to a preëxisting hypertension. Pregnant women fulfilling the above criteria were not included in this group. Realizing that the vessel trauma incident to a long standing hypertension eventually results in arteriosclerosis, we placed those patients fulfilling the above enumerated criteria in this group regardless of the presence of arteriosclerosis. It is felt that the type of blood pressure elevation and the character of the resulting vessel change are sufficiently distinctive to exclude the possibility of arteriosclerosis being the primary factor in the production of the heart disease. In other words, all patients placed in this group were considered as having essential hypertension with or without its complications, the presence or absence of the latter depending largely on the duration of the blood pressure elevation.

Arteriosclerotic Heart Disease and Coronary Artery Disease.—There were placed in this group those patients who exhibited definite evidence of arterial change, the senescent type of arteriosclerosis in the large majority of instances, usually with cardiac enlargement, with or without elevation of the blood pressure, and with definite evidence of a diminished cardiac reserve. In those cases exhibiting hypertension a careful study of numerous blood pressure determinations was made before placing them in this group. In all instances the diastolic blood pressure was found to be essentially normal or only slightly elevated in proportion to the systolic pressure, which was constantly high, in some cases the elevation being moderate, in others marked. It is felt that arteriosclerosis with the consequent rigidity of the vascular tree, so characteristic of old age, is responsible for this type of blood pressure elevation which is entirely different in both pathogenesis and character from that type previously discussed. It follows from these criteria that a majority of the patients in this group were of advanced age. However, there are also included in this category a fair number of patients in middle life exhibiting clinical evidence of myocardial weakness and failure in whom coronary artery disease was thought to be the etiological agent. The clinical picture portrayed by this type of heart disease manifestly lacks discreteness. In our series reliance was placed mainly on the past history of a probable coronary thrombosis, along with electrocardiographic evidence, or on electrocardiographic evidence alone in arriving at a diagnostic decision in these cases.

Syphilitic Cardiovascular Disease.—In the diagnosis of this type of heart disease, emphasis was placed largely on the discovery of one of the characteristic structural changes; namely, aortitis, aneurysm, or aortic insufficiency, or a combination, in the presence of a positive Wassermann reaction, of a positive history, or of lesions in other parts of the body pathognomic of a syphilitic infection. In all cases of aortic regurgitation, especially in young persons, a history of the presence or absence of past attacks of rheumatic fever, chorea, or recurrent tonsil-

litis was taken into consideration. A surprisingly small number of cases of syphilitic aortitis are represented in our series. It is our belief that this is largely due to the fact that syphilitic aortitis in the negro is only rarely attended by the classical symptoms of this condition and, as a result, these patients are not seen at this early stage of their disease. Aware of the difficulty in the diagnosis of this particular type of cardiovascular syphilis, especially if the symptoms are lacking and a moderate hypertension exists, we adhered to very rigid criteria in the compilation of this group. In patients fulfilling the criteria for other types of heart disease, the presence of a positive Wassermann reaction did not alter such a classification.

INCIDENCE OF HEART DISEASE

A review of the data presented in Table I indicates that organic heart disease occurs in 3.3 per cent of all patients seen in the Out-Patient Department of the John Sealy Hospital, and in 16.3 per cent of all patients seen in the Medical Division. A consideration of the incidence of organic heart disease in reference to race in the patients observed in the Medical Division reveals that 19.7 per cent of the negroes had heart disease, whereas only 11.5 per cent of the white patients were similarly afflicted. It follows from this analysis that in those patients who visit an out-patient department, heart disease occurs one and seven-tenths times more often in the negro than in the white race.

TABLE I

INCIDENCE OF ORGANIC HEART DISEASE

Number of Out-Patient Department Cases					49,880
Number of Medical Cases					10,188
Number of Cases of Organic Heart Disease					1,660
Percentage of Organic Heart Disease in All Cases					3.3
Percentage of Organic Heart Disease in Medical Cases					16.3
Classification of Cases According to Race and Sex:					
	White		Negro		
	Male	Female	Male	Female	
Medical Cases	2,570	1,682	3,188	2,748	
Heart Cases	301	187	640	532	
Percentage Showing Heart Disease	11.7	11.1	20.1	19.1	
Percentage of Organic Heart Disease in Total Whites					11.5
Percentage of Organic Heart Disease in Total Negroes					19.7
Percentage of Organic Heart Disease in Total Males					17.8
Percentage of Organic Heart Disease in Total Females					13.3

With reference to sex, 17.8 per cent of the males and 13.3 per cent of the females coming to the Medical Division had heart disease, indicating that in this clinic organic heart disease is one and three-tenths times of greater incidence in the male than in the female. Further resolution of this table discloses that 20.1 per cent of the negro males,

11.7 per cent of the white males, 19.1 per cent of the negro females, and 11.1 per cent of the white females had organic heart disease. Considering all types of heart disease the sex incidence in the respective races is practically the same, there being only a slight discrepancy between the negro males and females.

INCIDENCE OF THE ETIOLOGICAL TYPES

Reference to Table II reveals that of the 1,660 patients with heart disease 948 (57.2 per cent) were of the hypertensive type; 335 (20.2 per cent) were arteriosclerotic; 212 (12.7 per cent) were placed in the syphilitic group; 57 (3.4 per cent) permitted classification as of rheumatic origin; 41 (2.5 per cent) fell into the thyrotoxic class; 12 (0.7 per cent) were of congenital origin; 39 (2.3 per cent) were impossible of classification; and 16 (1.0 per cent), including 6 cases of subacute bacterial endocarditis, 8 of emphysema heart disease, and 2 of acute and chronic pericarditis, were classified as miscellaneous. There

TABLE II

FREQUENCY OF HEART DISEASE IN THE VARIOUS ETIOLOGICAL GROUPS

TYPE	NUMBER OF CASES	PER CENT	WHITE		TOTAL	NEGRO		TOTAL
			MALE	FEMALE		MALE	FEMALE	
Hypertensive	948	57.2	95	112	207	338	403	741
Arteriosclerotic	335	20.2	140	35	175	125	35	160
Syphilitic	212	12.7	31	2	33	132	47	179
Rheumatic	57	3.4	18	18	36	10	11	21
Thyrotoxic	41	2.5	1	13	14	6	21	27
Congenital	12	0.7	1	2	3	5	4	9
Miscellaneous	16	1.0	8	0	8	6	2	8
Unknown	39	2.3	7	5	12	18	9	27
Total	1,660	100.0	301	187	488	640	532	1,172

were included in this series 11 cases of angina pectoris, all complicating some other type of heart disease and all occurring in white patients. These statistics make it obvious that in this particular community we are concerned largely with three types of heart disease; namely, the hypertensive, the arteriosclerotic, and the syphilitic, these three groups constituting approximately 90 per cent of all cases of organic heart disease coming under observation. Rheumatic heart disease, an extremely important etiological group in many sections of the United States, in this locality plays a very minor rôle.

HYPERTENSIVE HEART DISEASE

In this locality, patients with this type of heart disease constitute by far the largest etiological group, 948 cases or 57.2 per cent of all the cases of organic heart disease. Of these 948 patients, 207 (12.4 per cent) were white patients and 741 (44.6 per cent) were negroes.

The incidence of hypertensive heart disease in the patients coming to the Medical Division is 12.5 per cent for the negro and 4.9 per cent for white patients, from which it seems to follow that the hypertensive type of heart disease is about two and one-half times of greater incidence in the negro than in the white race. Similar analysis of these data in a consideration of the influence of sex on the incidence of this etiological type reveals that of the 948 patients constituting this group 515 (31 per cent) were females and 433 (26.1 per cent) were males, the incidence for the patients seen in the Medical Division being 11.6 per cent for females and 7.5 per cent for males. Obviously in this clinic hypertensive heart disease is of one and one-half times greater incidence in females than in males. The greater incidence of hypertensive heart disease in the female is not generally appreciated, several standard textbooks stating the opposite to be true. Analysis of these same data as regards both race and sex reveals that the incidence of hypertensive heart disease in the patients coming to the Medical Division was as follows: negro males 10.6 per cent, white males 3.7 per cent, negro females 14.7 per cent, and white females 6.6 per cent. These figures suggest that in this type of heart disease the incidence is three and one-tenth times as great in the negro male as in the white male, and two and two-tenths times of greater incidence in the negro female than in the white female. It is further indicated that essential hypertension is one and eight-tenths times of greater prevalence in the white female than in the white male, whereas in the negro race the incidence in the female is only one and four-tenths times greater than that in the male.

ARTERIOSCLEROTIC HEART DISEASE

Patients with this type of heart disease comprise the second largest group in this series, 335 cases or 20.2 per cent of all the heart cases. Approximately 60 per cent of these cases exhibited hypertension. Of these 335 cases, 175 (10.5 per cent) were white patients and 160 (9.6 per cent) were negroes. The incidence in the medical cases for the arteriosclerotic type of heart disease with reference to race is 2.7 per cent for negroes and 4.1 per cent for white patients, from which it follows that this type of heart disease occurs one and one-half times more frequently in the white than in the negro race. Further analysis of these data in a consideration of the influence of sex on the incidence of this type of heart disease discloses that of these 335 patients there were only 70 (4.2 per cent) females as compared with 265 (15.9 per cent) males, the incidence in the medical cases being 1.6 per cent for females and 4.6 per cent for males. Manifestly this etiological type of heart disease occurs approximately three times as often in males as in females.

SYPHILITIC CARDIOVASCULAR DISEASE

Of the 1,660 cases of organic heart disease, 212 or 12.7 per cent fell into this category. With reference to structural changes this group is further divisible as follows: 162 cases of aortic regurgitation of which 102 occurred in negro males, 32 in negro females, 25 in white males, and 2 in white females; 37 aneurysms of which 24 occurred in negro males, 7 in negro females, and 6 in white males; 14 cases of syphilitic aortitis all of which occurred in the negro race, 6 in the males and 8 in the females. Considering all of the patients seen in the Medical Division of the Out-Patient Department, the racial incidence for this type of heart disease is 3 per cent for negroes as compared with 0.7 per cent for the white race. Conversely this type of cardiovascular disability is four times as frequent in the negro as in the white medical patient. A consideration of the incidence with reference to the various structural changes reveals that aneurysms occur with greater frequency in the negro as compared with the white race than does aortic insufficiency. A consideration of these statistics from the aspect of the relation of sex to the incidence of this etiological type reveals that among the medical patients the incidence for males is 2.8 per cent while for females it is only 1.1 per cent, indicating that in this locality at least this type of heart disease is of two and one-half times greater incidence in the male than in the female.

RHEUMATIC HEART DISEASE

The number of patients included in this series suffering with this type of heart disease is too small to justify the arrival at any conclusions as regards the influence of race or sex on the incidence of this etiological type. In this locality rheumatic heart disease like the arteriosclerotic type appears to occur more frequently in the white race than in the colored. As regards sex, the incidence is slightly higher in the female than in the male.

The low incidence of rheumatic heart disease in this community is readily explainable on the basis of the rare occurrence of the rheumatic series of infections in the South, a phenomenon in which climate appears to play a large part.

THYROTOXIC HEART DISEASE

In this clinic where hyperthyroidism is not frequently seen, this type of heart disease necessarily constitutes a relatively small group, 41 cases or 2.5 per cent of all the heart cases. It is, however, interesting to note that in this small group, too small perhaps to be of any comparative value, the incidence for this type of heart disease is greater in the negro (0.4 per cent) than in the white race (0.3 per cent). As would be expected, the incidence in females is greater than that in the males.

The infrequency of endemic goiter in this locality because of its situation on the seacoast seems to be an adequate explanation for the low incidence of thyrotoxic heart disease here as compared with more inland regions.

UNKNOWN HEART DISEASE

The group impossible of classification constituted 2.3 per cent of the heart cases. It is very probable that a fair number of the cases catalogued in this group formerly had hypertension, in view of the fact that they presented evidence of marked enlargement of the heart in the absence of valvular disease, a finding so characteristic of the hypertensive type, and a complete absence of other discernible etiological factors. Also included in this group are a number of cases, practically all negro males, who exhibited marked cardiac enlargement, congestive heart failure in the majority of instances, a strongly positive blood Wassermann reaction, and a striking absence of the characteristic structural lesions of syphilitic heart disease. Necropsy on a number of these cases shed no further light on an etiological diagnosis. It is very likely that they belong in the syphilitic group.

COMPARISON

Few statistics are available to enable a comparison of the incidence of heart disease in various sections of the United States to be made. Davis and Thoroughman[4] reported that 3.7 per cent of all admissions to the University Division of the Grady Hospital of Atlanta, Georgia and 21.7 per cent of those admitted to the Medical Services had organic heart disease. In an interpretation of these data it should be remembered that only negroes are admitted to this hospital. In Stone and Vanzant's series[1] 3.6 per cent of all hospital admissions and 16 per cent of all admissions to the Medical Services (of the John Sealy Hospital in Galveston) had organic heart disease. Coffen[5] of Portland, Oregon reported that of 13,258 medical patients admitted to six different hospitals 26 per cent were afflicted with heart disease.

The available statistical matter on the incidence of the etiological types of heart disease accumulated from widely separated sections of the country should lend itself to a very valuable as well as interesting study in comparison. However, owing to the discrepancy of the diagnostic criteria employed for certain types of heart disease by the different authors, an exact comparison is made very difficult. The fairly universally accepted criteria for the diagnosis of syphilitic, rheumatic, and thyrotoxic heart disease permits accurate comparison of these etiological types. The difficulty arises when a comparison of the arteriosclerotic, the coronary artery disease group, and the hypertensive groups is attempted, as in many instances these groups are combined and designated as arteriosclerotic or as arteriosclerotic plus hypertension.

TABLE III

COMPARISON OF REPORTED STATISTICS

	VIRGINIA	NEW YORK CITY	NEW ENGLAND	ROCKY MOUNTAINS	TEXAS		AVERAGE
					STONE AND VANZANT	OURS	
No. cases	300	1,000	2,421	867	915	1,660	
	%	%	%	%	%	%	%
Rheumatic	15.6	42.7	29.3	44.0	7.3	3.4	5.3
Arteriosclerotic	32.4	22.3	26.3	21.1	13.7	20.2	16.9
Hypertensive	32.6	—	21.7	14.9	47.7	57.2	52.4
Syphilitic	7.8	8.6	2.7	1.1	19.3	12.7	16.0
Thyroid	2.6	—	2.1	9.3	1.3	2.5	1.9
Angina pectoris	6.6	—	10.9	—	2.3	—	—
Congenital	0.7	—	1.1	1.1	0.7	0.7	0.7
Unknown	1.6	17.8	2.2	7.3	4.9	2.3	3.6
Miscellaneous	—	8.6	1.6	0.9	1.3	1.0	1.1
Subacute bacterial endocarditis	—	—	1.4	0.2	1.5	0.3	0.9

The use of that type of classification does not permit further segregation of the hypertensive cases into those in which the arteriosclerosis was a secondary change and those in which the condition was primary. In this communication an attempt has been made to distinguish between the different types of hypertension and to catalogue them in separate groups.

In Table III, taken from the report of Viko[6] with the addition of data accumulated by this study, there is presented a comparison of the relative incidence of the etiological types of heart disease in widely separated sections of the United States.

As was emphasized in the introduction of this communication, the incidence of heart disease, particularly the relative incidence of the etiological types, in a locality will vary, depending upon the source of the material—that is whether the statistics were gathered from a study of private, hospital, or dispensary patients. Reference to Table III reveals a discrepancy in the data presented by Stone and Vanzant and the results obtained from our study. This discrepancy confirms the truth of the statements made in the introduction. The difference is disclosed mainly in the comparison of the hypertensive group (47.7 per cent compared with 57.2 per cent), the arteriosclerotic (13.7 per cent compared with 20.2 per cent), and the syphilitic (19.3 per cent compared with 12.7 per cent). These differences are readily explainable by the fact that the cardiac disability incident to the hypertensive and the arteriosclerotic types is seldom as extreme as in the syphilitic group and consequently a fewer number of the former groups demand hospitalization as compared with the latter. Another factor which accounts for the greater number of hypertensive cases in our series is the larger percentage of negroes in our study who, as we have already shown, have a much higher incidence of hypertensive heart disease than do white patients.

As regards a comparison of the incidence of the etiological types of heart disease in this locality with similar statistics from other sections of the country, our results do not materially alter the conclusions drawn by Stone and Vanzant, but further emphasize the high incidence of syphilitic and hypertensive heart disease and the extremely low incidence of rheumatic heart disease. The high incidence of these two types of heart disease is accounted for largely by the factor of race, a large number of negroes being included in both studies.

Perhaps the most outstanding fact that appears from this study is the extremely high incidence of organic heart disease as a whole in the negro as compared with his white brother. One becomes even more impressed following a comparison of the various etiological types in the two races. It is generally known that syphilitic heart disease is of much higher incidence in the negro than in the white race, usually attributed to the fact that syphilis is of greater prevalence in that race.

However, it is quite possible that this is not the only factor involved. On the contrary, it is not generally recognized that hypertensive heart disease is of so much greater prevalence in the negro race, being in this study two and one-half times more frequent. This rather startling fact opens a fertile field for investigation. Were it possible definitely to ascertain the reasons for this marked discrepancy, the riddle of hypertension would be nearer solution. Arteriosclerotic heart disease alone occurred with greater frequency in white patients than in those of the negro race. We believe that this is probably attributable to the fact that the average age of death in the negro race is much lower than in the white race, and, as a result, a smaller number of negroes reach that period of life in which this type of heart disease occurs.

A detailed discussion of all possible causative factors which might account for the much higher incidence of heart disease in the negro race will be presented in a future communication.

SUMMARY AND CONCLUSIONS

1. The incidence of organic heart disease in the Out-Patient Department of the John Sealy Hospital of Galveston, Texas is 3.3 per cent for all admissions and 16.3 per cent for those patients observed in the Medical Division.

2. Organic heart disease as seen in this clinic is of one and three-tenths times greater incidence in the male than in the female, and of one and seven-tenths times greater incidence in the negro than in the white race.

3. The hypertensive group (57.2 per cent), the arteriosclerotic group (20.2 per cent), and the syphilitic group (12.7 per cent) constitute 90 per cent of all cases of organic heart disease coming under observation.

4. Hypertensive heart disease, as seen in this dispensary, is of one and one-half times greater incidence in the female than in the male and is of two and one-half times greater incidence in the negro than in the white race.

5. Arteriosclerotic heart disease occurs three times as frequently in the male as in the female, and one and one-half times as frequently in the white as in the negro race.

6. Syphilitic heart disease is two and one-half times as prevalent in the male as in the female and of four times greater incidence in the negro than in the white race.

7. The incidence of rheumatic heart disease among all cases seen in the Medical Division is only 3.4 per cent.

8. The incidence of heart disease and particularly the relative incidence of the various etiological types in a community varies with the source of the material from which the data are compiled.

9. Attention is called to the much greater prevalence of heart disease in the negro race.

The writers wish to acknowledge their indebtedness to Dr. Joseph Kopecky who originally started the filing system which made this study possible.

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THE LARGE Q-WAVE OF THE ELECTROCARDIOGRAM. A CORRELATION WITH PATHOLOGICAL OBSERVATIONS*

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THE presence of a large Q-wave in Lead III has been noted by Pardee[1, 2] and Levine[3] in cases of coronary occlusion. Subsequent analysis of electrocardiograms at Montefiore Hospital confirmed their observations and also indicated that the large Q-wave was a frequent electrocardiographic sign in this condition. As the initial part of the QRS deflection† probably corresponds to the excitation of the septum and adjacent apices of the two ventricles (Lewis[4]), it appeared to us that damage to the septum with involvement of the minor conducting divisions supplying the apical regions, might be responsible for the production of the large Q-wave.

THE FREQUENCY OF THE LARGE Q-WAVE

Before attempting a correlation with pathological material, the frequency of the large Q-wave was determined in the electrocardiograms of the last 140 cardiac patients at Montefiore Hospital. The records of the 35 necropsied cases considered in the correlation are excluded from this group. Pardee's criterion for a large Q-wave was adopted: that is, a negative wave of more than 25 per cent of the maximum deflection in whichever lead the latter occurred. In Pardee's collection of 227 records obtained from healthy adults with apparently normal hearts, only 2 presented a large Q-wave in Lead III.

Occasional difficulty was encountered in interpreting a small initial upward peak, especially in Lead III of left axis deviation records because of muscular tremors or oscillatory waves of auricular fibrillation. This difficulty was usually solved by scrutinizing all the complexes in the lead. Moreover, if the initial part of the QRS complex in Lead II was more negative than in Lead I, it was inferred that a doubtful preliminary deflection in Lead III was also negative.

Of the 140 patients with heart disease, 30 were clinically suspected of suffering from coronary artery disease; the records of 13 of these showed a large Q-wave in Lead III and another presented a large Q-wave in Lead II only. In this group of 30, 27 records showed left axis deviation. The electrocardiograms of the remaining 110 cases were classed according to axis deviation. None of the 30 with normal

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†Following Lewis' terminology, the Q-wave denotes an initial negative deflection of the QRS complex while the R-wave denotes an initial positive deflection.

axis deviation revealed a large Q-wave in any lead. In the 40 records with right axis deviation, a large Q-wave only in Lead III was observed in but 2, both being from children with congenital pulmonic

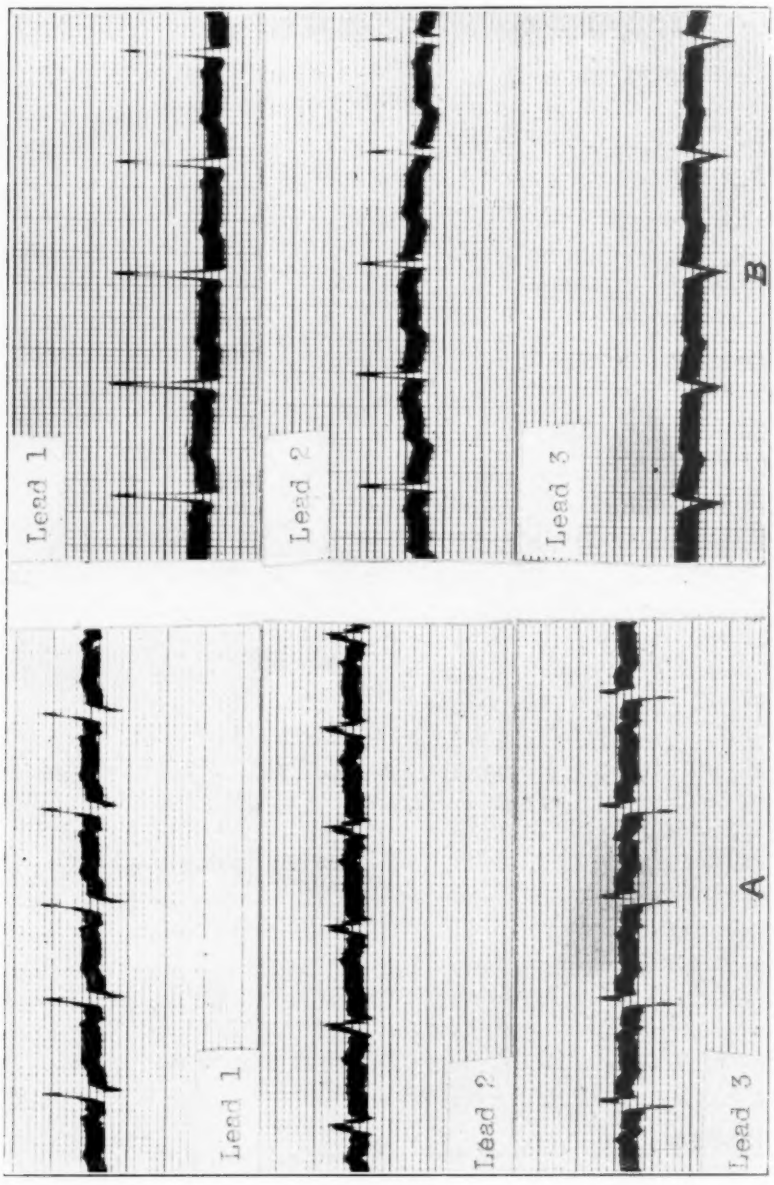

Fig. 1.—*A*, Case 6; *B*, Case 8. Both records show left axis deviation with a large Q_3.

stenosis. Two of the 40 records of left axis deviation showed a large Q-wave in Lead III and one other showed a small Q-wave in Lead III. These 3 records were obtained from children with rheumatic mitral and aortic valvular lesions, aortic insufficiency predominating.

It is seen from these statistics that a large Q-wave in any lead of the electrocardiogram (excluding cases of congenital and advanced rheumatic heart disease) is unusual except in cases of myocardial involvement consequent upon coronary artery disease. Inasmuch as the great majority of records from cases suspected of myocardial infarction show left axis deviation, special attention is directed to the third lead in this type of record. In cases without myocardial infarction this lead usually shows a distinct initial upward peak or R-wave of considerably more than 5 per cent of the maximum QRS deflection before joining the principal downward deflection or S-wave (Fig. 3*A*). If the upward peak is less than 5 per cent of the maximum QRS deflection, the preliminary deflection cannot be classified (Fig. 3*B*). On the other hand, in the cases of myocardial infarction, this lead most frequently shows either a very large Q-wave due to the fusion of the initial downward deflection with the principal inverted deflection or no Q at all (Fig. 1).

CORRELATION OF ELECTROCARDIOGRAMS WITH PATHOLOGICAL MATERIAL

Thirty-five hearts from patients who died on the Medical Service during the past two years were then examined. The cases were not selected except for the exclusion of congenital and uncomplicated rheumatic hearts as well as those with records of major intraventricular conduction disturbance as differentiated by a QRS interval over .12 sec. In this particular type of electrocardiogram, there is represented probably a disturbance of conduction in either main branch, and minor aberrations in excitation cannot therefore be evaluated. Most of the patients suffered from hypertension, antecedent or persistent, with the chronic arteriosclerotic complications. The remainder of the series comprised 2 cases of syphilitic aortitis, 2 cases of polycythemia vera, and 2 cases of rheumatic carditis with concomitant hypertension. The majority were followed in the hospital for a few months and had several electrocardiograms taken. Successive electrocardiograms did not usually show much variation, since additional acute occlusions were infrequent. In correlating the records with the cardiac changes, due consideration was given to the lapse of time between the last record and the date of necrospy. The last record was taken within the month before death in all but 3 cases.

On gross examination the hearts were scrutinized particularly for the nature and site of myocardial damage with particular reference to interventricular septal involvement. Microscopical studies were made when gross inspection was inconclusive. In most of the cases, the myocardial damage consisted of healed infarcts or scattered patches of fibrosis resulting from occlusion of one or more of the principal coronary arteries.

In Table I are listed 12 cases with electrocardiograms of left axis deviation and a large Q_3 (Fig. 1). Myocardial damage with involvement of the septum posteriorly, and in most instances anteriorly as well, was present in all the hearts. Case 12 showed a recent infarction of the posterior wall of the left ventricle and a recent thrombosis in the right coronary artery. Grossly the septum appeared normal and on microscopical examination only some small areas of fibrosis were seen. In the successive electrocardiograms of Case 12, a large Q_3 was observed six months prior to death; this was absent three months later but reappeared five days before death from the acute coronary thrombosis. This case was also the only one demonstrating a transient large Q_3.

TABLE I

LEFT AXIS DEVIATION WITH LARGE Q_3*

CASE NO.	PART OF SEPTUM INVOLVED	INITIAL WAVE OF QRS			MAXIMUM QRS DEFLECTION
		LEAD I	LEAD II	LEAD III	
1	Lower third, anteriorly and posteriorly	+ 8	− 7	−16	16
2	Lower posterior	− 1	− 2	−12	24
3	Lower half, anteriorly and posteriorly	− 1	− 2	− 6	17
4	Diffuse fibrosis, especially posteriorly	− 1	− 0.5	−13	14
5	Lower third, anteriorly and posteriorly	− 1	− 1	− 6	15
6	Lower two-thirds, posteriorly	+ 6	− 1	− 5	7
7	Diffuse fibrosis of entire septum	+ 5	− 2	− 2.5	5
8	Lower two-thirds, posteriorly	+12	− 1	− 4	12
9	Diffuse fibrosis of entire septum	+12	+ 7	−11	12
10	Lower half, anteriorly and posteriorly	+20	+ 1	−20	23
11	Diffuse fibrosis with necrosis in center beneath aortic ring	+ 8	− 1	−11	12
12	Slight fibrosis, especially posteriorly	− 5	− 1	− 9	12

*All of these hearts showed healed myocardial infarcts or scattered areas of fibrosis subsequent to coronary artery occlusions. The extent of the septal involvement is given in the table. In the measurement of the initial wave of the QRS complex in each lead, the value of either the Q or the R is given in 10^{-4} volts. The value of the maximum QRS deflection is taken from the lead in which it occurred, regardless of whether the deflection was upright or inverted.

Table II comprises 3 cases with tracings showing normal axis deviation and a large Q_3 (Fig. 2A). In Case 14, Q_1 was larger than Q_3. All three presented healed myocardial infarcts including the lower part of the septum anteriorly and posteriorly.

TABLE II

NORMAL AXIS DEVIATION WITH LARGE Q_3†

CASE NO.	PART OF SEPTUM INVOLVED	INITIAL WAVE OF QRS			MAXIMUM QRS
		LEAD I	LEAD II	LEAD III	
13	Lower half, anteriorly and lower fourth, posteriorly	+5.5	+8.5	−3	8.5
14	Lower third, anteriorly and posteriorly	−3	−2	−1	3
15	Lower third, anteriorly and posteriorly	−1	−1.5	−2	4

†A healed myocardial infarct resulting from coronary artery occlusion was found in each of the three hearts.

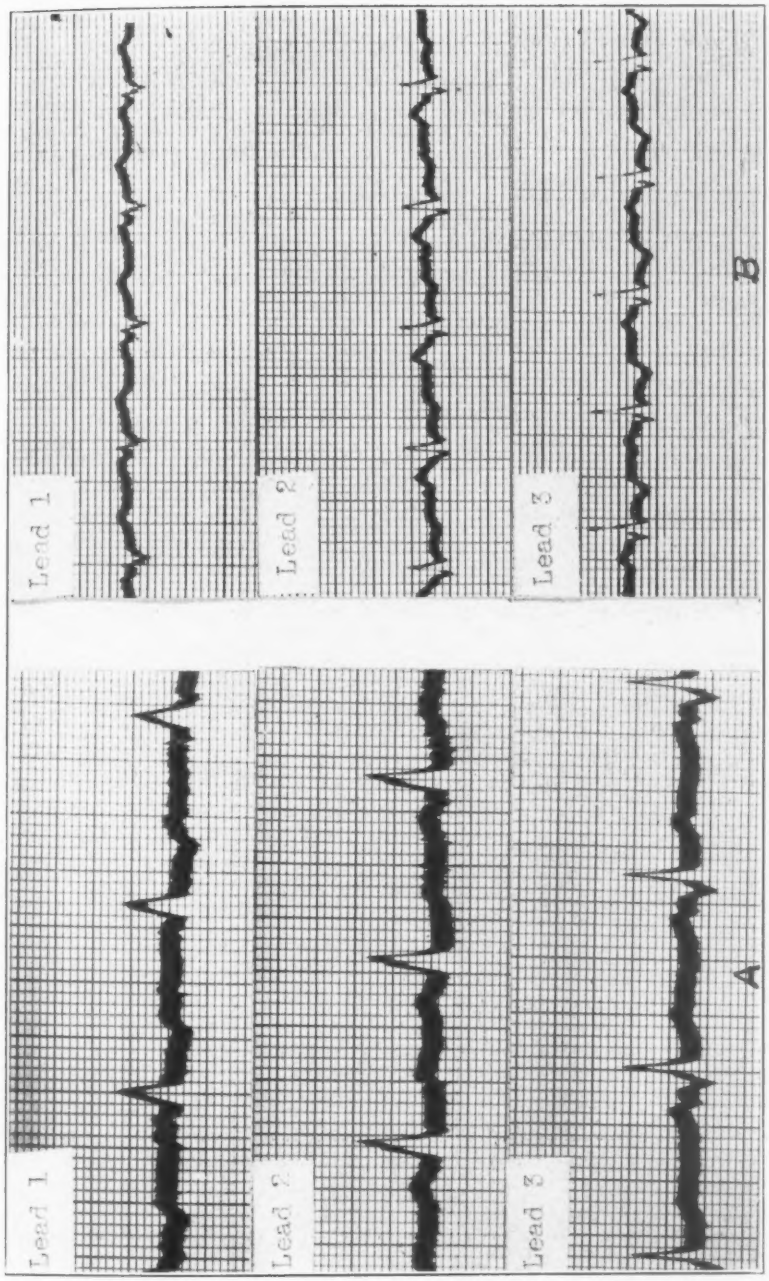

Fig. 2.—*A*, Case 13. Normal axis deviation with a large Q_3. QRS interval .11 sec. *B*, Case 16. Right axis deviation with a large Q_2 and Q_3. QRS interval .11 sec.

In Table III are listed 2 cases with records of right axis deviation and a large Q_3 (Fig. 2*B*). In Case 16, Q_2 was slightly larger than Q_3. Myocardial damage with extensive involvement of the anterior and posterior portion of the septum was present in each heart.

TABLE III

RIGHT AXIS DEVIATION WITH LARGE Q_3*

CASE NO.	PART OF SEPTUM INVOLVED	INITIAL WAVE OF QRS			MAXIMUM QRS
		LEAD I	LEAD II	LEAD III	
16	Entire left ventricular surface of septum	+1	−2.2	−2	6
17	Lower half, anteriorly and posteriorly	+5	+3	−2	5

*Both hearts showed myocardial scars and coronary artery closures.

Table IV contains 16 cases with records of left axis deviation and a positive preliminary deflection in Lead III of more than 5 per cent of the maxium deflection (Fig. 3*A*). In the first five cases (Cases 18 to 22) there was evidence of coronary occlusion and myocardial damage without any involvement of the septum. In the following 8 cases (Cases 23 to 30) the septum as well as the rest of the myocardium

TABLE IV

LEFT AXIS DEVIATION WITH POSITIVE PRELIMINARY DEFLECTION IN LEAD III*

CASE NO.	PART OF SEPTUM INVOLVED	INITIAL WAVE OF QRS			MAXIMUM QRS
		LEAD I	LEAD II	LEAD III	
18	None	+14	+12	+6	15
19	None	− 1	+ 7	+2	9
20	None	− 2.5	+ 9	+7	14
21	None	+ 0.5	+ 1.5	+2	14
22	None	− 1.5	+ 3	+5	27
23	None	+ 8	+ 5	+1.7	9
24	None	− 1	+ 1	+2	23
25	None	− 1	+ 9	+3.5	13
26	None	+ 8	+ 3	+1.5	9
27	None	− 1	+18	+2	19
28	None	− 1	+ 3	+2.5	20
29	None	− 1	+ 9	+1.3	12
30	None	+17	+13	+2	17
31	Extreme anterior margin	+15	+ 3	+2	16
32	Lower third, anteriorly	+ 7	+ 6	+4	16
33	Diffuse fibrosis of lower half	+ 6	+ 2	+1.5	9

*The hearts of Cases 18 to 22 revealed coronary occlusions and healed infarcts or fibrosis in the left ventricle without any septal involvement. In the heart of Case 23, an occlusion of a small branch of the left circumflex artery was seen, but the myocardium appeared normal. In the hearts of Cases 24 to 30, the myocardium was intact although there was slight to moderate sclerosis of the coronary vessels. The hearts of Cases 31 to 33 presented healed myocardial infarcts.

appeared intact. The last 3 cases (Cases 31 to 33) showed healed myocardial infarcts with septal involvement. Case 33 alone revealed damage in the posterior part of the septum.

In Table V are listed 2 cases with electrocardiograms of left axis deviation and unclassified preliminary deflection in Lead III. The

record of Case 34 contained a very small initial upward deflection in Lead III of only 4 per cent of the maximum deflection (Fig. 3*B*). In Case 35, the preliminary deflection in Lead III showed a pronounced

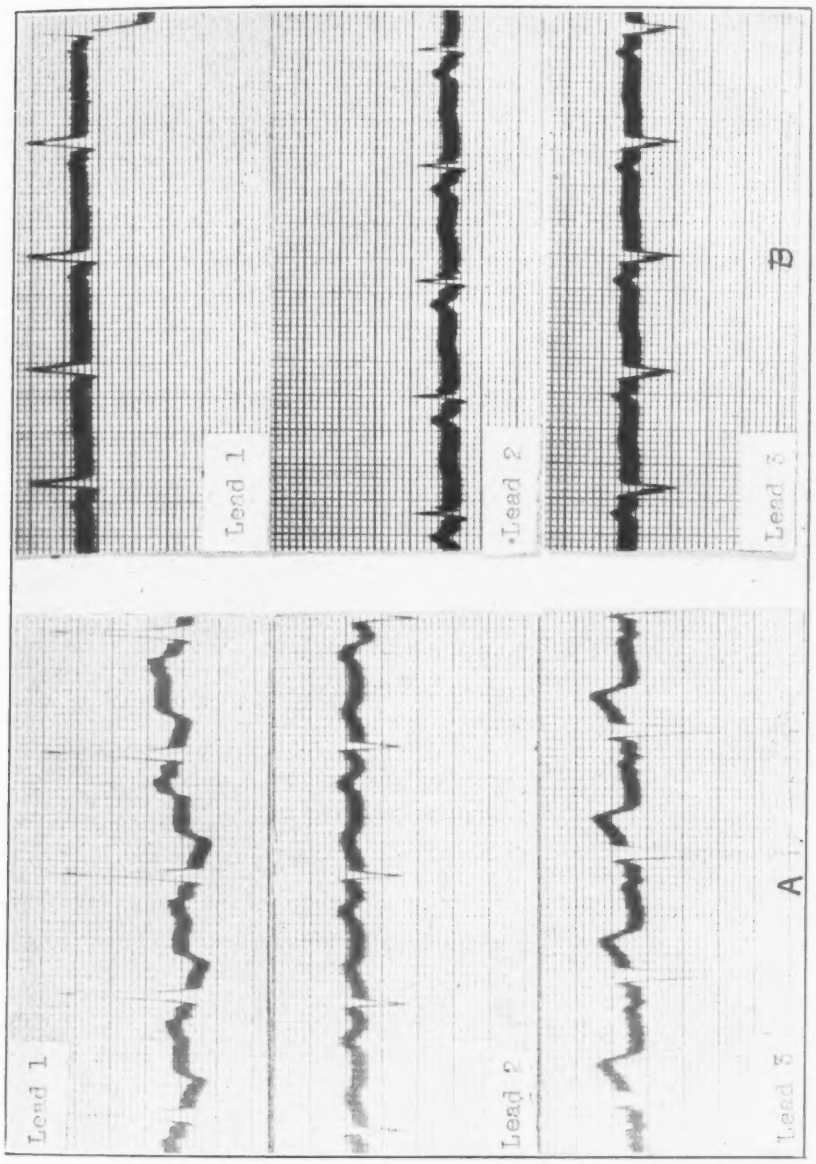

Fig. 3.—*A*, Case 24. Left axis deviation with a positive preliminary deflection in Lead III equivalent to 8 per cent of the maximum QRS deflection. This record represents the minimum ratio of R_3 to maximum QRS in the entire group of Table III. *B*, Case 34. Left axis deviation with an unclassified preliminary deflection in Lead III. R_3 is 4 per cent of the maximum QRS.

change during an intervening fifteen months' period, the second record having been taken one month before death. Although this last record did not present any Q_3, its preliminary deflection was definitely altered (Fig. 4). Healed myocardial infarcts with extensive septal involvement were present in both cases.

In consideration of the variability of the coronary circulation evident from the different sites of infarction with occlusion of the same

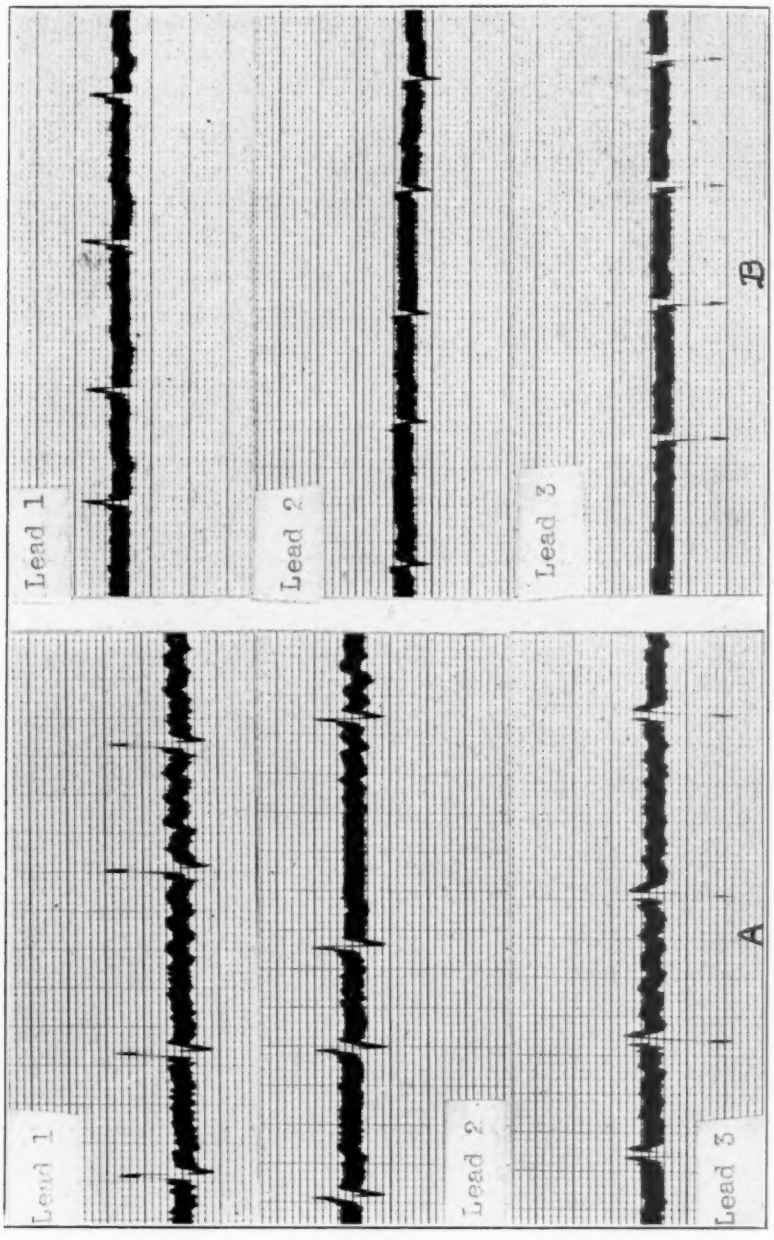

Fig. 4.—*A*, Case 35, sixteen months before death. Left axis deviation with a definite (20 per cent) preliminary R in Lead III that is partially obscured by the oscillatory waves of auricular fibrillation. *B*, the same case, one month before death. R_3 is smaller (12 per cent) and splintered.

vessels, and of a probable similar anatomical variability of the specialized conducting system, a more precise localization of the septal damage was not attempted. All of the 17 cases with a large Q_3 revealed septal involvement, at least in the posterior portion. In the

TABLE V

LEFT AXIS DEVIATION WITH UNCLASSIFIED PRELIMINARY DEFLECTION IN LEAD III*

CASE NO.	PART OF SEPTUM INVOLVED	INITIAL WAVE OF QRS			MAXIMUM QRS
		LEAD I	LEAD II	LEAD III	
34	Lower half, anteriorly and posteriorly	−0.8	−1.4	+0.3	8
35	Lower half, anteriorly and posteriorly	−0.5	+0.5	+0.8	7

*Both hearts showed coronary artery occlusions with healed infarcts.

16 cases without a large Q_3, only one showed involvement of the posterior portion of the septum. No attempt was made to correlate the pathology in the remaining 2 cases (Cases 34 and 35) with their unclassified electrocardiograms.

COMMENT

These findings indicate that a large Q_3 is associated with damage in the septum, particularly in the posterior portion. The frequency of the large Q_3 probably depends on the proximity of the septum to the most frequent sites of infarction. The large Q_3 ensues in the majority of instances when the resultant apical infarction, subsequent to occlusion of the left anterior descending branch, includes the lower posterior part of the septum. When the right coronary artery is occluded, the infarction in the posterior wall of the left ventricle usually involves the adjacent posterior part of the septum. The large Q_3 was observed in 9 cases where the sole infarct occurred at the apex as well as in 4 cases where the sole infarct occurred in the superior or middle part of the posterior wall of the left ventricle. Accordingly, this excludes the possibility that the large Q_3 is a consequence of one particular site of infarction in the walls of the left ventricle.

Six cases recorded a large Q_2 which in 2 was even greater than the large Q_3; while in another Q_1 was the largest. Myocardial infarction with septal involvement was present in all 7. While these data are insufficient to draw any conclusions, it seems that a large Q_1 or Q_2, normally infrequent, may have the same significance as the large Q_3.

The large Q_3 is especially important because it is the most frequent electrocardiographic sign during the chronic period of myocardial infarction. Sometimes it is the only graphic clue to the pathological condition present in the heart. During the acute period of myocardial infarction, the large Q_3 and the other characteristic signs commonly occur together; but in the period subsequent to the acute coronary thrombosis the R-T segment usually becomes iso-electric and the T-wave inversion becomes absent or limited to either Lead I or Lead III. This is borne out in our necropsied cases of myocardial infarction or fibrosis, predominantly of chronic nature; a large Q_3 is present in 17, whereas a negative T in at least two leads is found in 8, and an abnormal R-T segment in 6. Electrocardiograms with QRS intervals

over .12 sec., such as occur in bundle-branch block or arborization block, were not included in this study. Although such records are also indicative of coronary artery disease, they are not seen as often as those with normal QRS intervals.

An inspection of the cases of coronary thrombosis reported by others presents some similar findings. On examining the 82 electrocardiograms of Levine's[3] series, a large Q_3 is found in approximately 40 per cent, including the 4 cases where definite mention is made of septal infarction. In Barnes and Whitten's[5] series, there is no instance where a large Q_3 occurs without septal involvement. However, in 3 cases in which involvement of only the anterior part of the septum is described, no abnormal Q_3 is seen. The findings in the last 3 cases thus correspond to our observations in Case 31 and Case 32.

Some of the electrocardiograms of Levine's series, taken shortly after an acute occlusion, showed a large Q_3 which subsequently disappeared. A transient large Q_3 was present in only one of our cases (Case 12) probably because our patients were not usually observed in the period immediately following the acute thrombosis. Temporary circulatory disturbance of that part of the septum adjacent to an area of infarction may be responsible for the production of a large Q_3 which later disappears, possibly due to the development of a compensatory collateral circulation. Consequently, a transient large Q_3 may also be considered as indicative of myocardial involvement. Pardee[2] observed a transient large Q_3 in the records of a boy during a bout of acute rheumatic carditis. This may have been due to an acute inflammatory lesion in the septum.

It is interesting to note that the experimental work in dogs yields some suggestive observations. Rothberger and Winterberg[6] studied the electrocardiographic changes following severance of the anterior and posterior divisions of the left bundle-branch. When either division was cut, no widening of the QRS complex occurred. After cutting the posterior primary division, they noticed a prominent increase of the R in the ano-esophageal lead. In their observations they did not include any comparatively small alterations in the early part of the QRS complex. However, on comparing their records from four experiments in which the posterior division was divided, a small Q which is absent in the ano-esophageal lead of the control records, is seen in the ano-esophageal lead of three of the four postoperative records. Otto's[7] records also demonstrate the appearance of a small Q in the axial lead (Lead II) after section of the posterior division. Although a large Q was not recorded following these operations, nevertheless the change from a preliminary upward to a small downward deflection may possibly be sequential to a similar aberration of ventricular excitation in the dog.

THEORETICAL CONSIDERATIONS

Before considering the origin of the large Q_3, it is necessary to investigate the influence of ventricular hypertrophy and heart position upon the deflections occurring during the various periods of ventricular activation. Lewis[4] concluded that the inscription of Q and the beginning of R corresponded in time to the excitation of the septum, right papillary muscle, apices of the two ventricles and immediately adjoining areas; the most prominent part of R, he ascribed to activation of the mass in the walls; and the last part of the QRS complex, predominantly to basilar excitation. While these conclusions were deduced from experimental work in dogs, they are probably even more applicable to man. Because of the relatively larger dimensions of the endocardial surfaces of the human ventricles, a greater proportion of time is required to distribute the excitation wave to the various endocardial regions. Therefore, the septum, adjacent anterior and

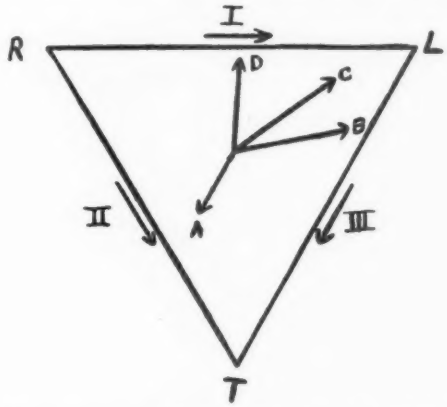

Fig. 5.—The electrical axes calculated from four electrocardiograms at .02 sec. and drawn to the same scale. *A* from Fig. 3*A*; left axis deviation with a preliminary R_3. *B* from a record of right axis deviation with a small Q_3. *C* from Fig. 1*A*; left axis deviation with a large Q_3. *D* from Fig. 2*B*; right axis deviation with a large Q_2 and Q_3.

R, L, and T represent respectively, the right arm, left arm, and left leg electrodes. The arrows indicate the directions associated with positive deflections in the three leads.

posterior walls, and adjacent apices of the two ventricles, being nearest to the bundle branches, would most likely be activated first. The anterior and posterior walls, by producing potential differences during activation that lie perpendicular to the frontal plane of the three electrodes, hardly affect the standard electrocardiogram and their influence may consequently be disregarded.

In the electrocardiograms of left axis deviation from cases uncomplicated by myocardial damage, the preliminary deflection is usually opposite to the main deflection, so that a small Q is most often present in Lead I and a small R in Lead III. In hearts with this type of record, the septum and adjacent inferior portions of both ventricles are

frequently displaced to the right by the relatively greater left ventricular hypertrophy. This is best seen *in situ* at post-mortem examination of cases with cardiac hypertrophy secondary to hypertension. The displacement of these regions, first activated, thus corresponds, in general, to the direction of the early electrical axes which are inclined downward and to the right as calculated from the initial negative deflection in Lead I and positive deflection in Lead III (Fig. 5*A*).

If one excludes cases of myocardial infarction, right axis deviation electrocardiograms usually show a positive preliminary deflection in Lead I and a small Q in Lead III, both being in opposite phase to the principal deflection. In these cases the relatively greater right ventricular hypertrophy causes a displacement of the septum and adjacent inferior portions upward and to the left, and the heart often rotates around its long axis so that the left ventricle lies more posteriorly, with the right ventricle forming almost the entire anterior cardiac surface. In advanced mitral stenosis this alteration of relations is particularly noticeable. The rotation and displacement of the septum and adjoining apical regions upward and to the left thus approximately corresponds to the direction of the early electrical axes calculated from the positive deflection in Lead I and the negative deflection in Lead III (Fig. 5*B*). This alteration, particularly marked on post-mortem examination of several hearts with congenital pulmonic stenosis, may explain the large Q_3 recorded in their electrocardiograms. In children and young adults with advanced rheumatic mitral and aortic lesions producing hypertrophy of both chambers, a similar displacement of the lower part of the septum is frequently present. However, some of these cases record electrocardiograms of left axis deviation due probably to the later excitatory preponderance of the lateral wall of the left ventricle. Hence the large Q_3, recorded in advanced rheumatic heart disease, may be due to considerable septal displacement and therefore does not necessarily indicate any aberration in ventricular excitation such as occurs with myocardial infarction.

Pardee[2] observed that a large Q_3 occasionally ensues from the displacement of the heart upward and to the left because of elevation of the diaphragm during deep expiration and at times even during pregnancy. Rotation of the early and later electrical axes upward and to the left occurs and is sometimes represented by the large Q_3. The alteration of the deflections with respiration is usually most marked in Lead III, for the electrical axes are most frequently directed approximately perpendicular to the line of this lead and consequently their projections on this line, representing the Lead III deflections, show the greatest variation. Einthoven[8] was the first to explain this phenomenon. The influence of deep expiration must therefore be considered before interpreting electrocardiograms with a large Q_3.

Our interpretation of the presence of a large Q_3 secondary to myocardial infarction is based on a minor aberration in ventricular activation. Assuming that the septum is so injured that the descending divisions to the left apex are principally involved, then the downward directed potential differences ordinarily generated by excitation at the medial part of the left apex are no longer recorded during the early period of the QRS deflection. Accordingly, the remaining upward directed potential differences in this period are no longer neutralized, and the electrical axes of the early intervals incline more definitely upward and with greater potential values. This is represented in the electrocardiogram by a prominent early negative deflection in the two semivertical leads (Leads II and III) (Fig. 5*D*). Because of the rich intraventricular anastomoses of the so-called Purkinje network, the excitation of the apex is only slightly delayed. Pronounced widening of the QRS interval is not produced, for, despite this delay, the excitation of the apex probably occurs within the time required for complete excitation of the more distant basilar portions of the ventricles.

The above explanation pertains to the large Q_2 or Q_3 recorded in the electrocardiogram with any type of axis deviation. Left axis deviation records of myocardial infarction, in particular, frequently present in Lead III a very large Q due to the fusion of the negative initial deflection with the negative main deflection. In such instances, the activation of the hypertrophied left ventricular musculature produces greater potential differences directed upward and toward the left, especially during the later intervals. Hence both early and later axes incline upward as well as to the left and lie approximately parallel to the line of Lead III. With the electrical axes lying in this direction, Q_3 is the larger, although Q_2 is usually also present (Q_2 is present in 10 of our 12 records of left axis deviation with a large Q_3) (Fig. 5*C*).

The investigation of our pathological material and the slight evidence from the experimental work in dogs suggest that injury to the smaller divisions in the posterior portion of the septum is particularly responsible for the development of this characteristic Q-wave. It is possible that the anterior subdivisions supply principally the anterior walls where activation does not affect the standard electrocardiogram significantly.

SUMMARY

(1) The frequency of the large Q-wave was investigated in the electrocardiograms of 140 patients with various types of heart disease. A large Q_3 was observed in the records obtained from 13 patients suspected of coronary artery disease, 3 patients with advanced rheumatic heart disease, and 2 patients with congenital pulmonic stenosis.

(2) The records of an additional group of 35 cases which came to necropsy were examined and a large Q_3 was found in 17 of the 27 cases with evidence of myocardial infarction or fibrosis; in the remaining 8 cases in which there was no myocardial damage, none recorded a large Q_3.

(3) A correlation of the electrocardiograms with the pathological findings indicates that:

a) The large Q_3 is the most frequent electrocardiographic sign of coronary artery disease during the chronic period.

b) The large Q_3 in myocardial infarction or fibrosis is probably due to involvement of the septum, particularly in its posterior portion.

(4) A theoretical interpretation of the production of the large Q is presented.

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THE NATURE OF EXPERIMENTAL FLUTTER AND FIBRILLATION OF THE HEART*†

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ARGUMENT

SEVERAL theories have been advanced to explain auricular and ventricular fibrillation. One of the earliest to be proposed was by Kronecker[1] who suggested the existence of a coördinating center in the interventricular septum of the heart. Puncture of this center was supposed to be followed by incoördination of myocardial contraction, manifested as fibrillation. MacWilliam[2] showed that it was unnecessary to assume the existence of such a center because he could produce fibrillation in an excised mass of muscle taken from a place at some distance from the supposed location of the center. MacWilliam suggested instead that fibrillation was due to a disturbed relation between the refractory phase, which was shortened, and conduction time, which was prolonged. The contraction wave in passing through the muscle mass thus encountered some muscle bundles which had recovered before the others. These contracted earlier and resulted in incoördinated myocardial activity. A somewhat similar theory was proposed by Winterberg[3] who suggested that fibrillation was due to multiple foci, causing numerous simultaneous or nearly simultaneous local contractions and that these prevented a coördinated contraction of the chamber of the heart as a whole. This theory was subjected to experimental analysis by Rothberger and Winterberg[4] who recorded simultaneously the local electrical and mechanical oscillations from two widely separated points of the fibrillating ventricle. It was found that these oscillations, from two different points, were rhythmic for short periods in some of the records. Such a relationship is difficult to correlate with activity due to multiple foci acting independently at the same time and Rothberger and Winterberg[4, 5] then proposed a modification of the theory. The modified theory supposes that both flutter and fibrillation are forms of tachysystole due to impulses from one or more ectopic foci. It is emphasized that one such ectopic focus may be sufficient to produce this phenomenon. The gross appearance of a fibrillating or fluttering chamber is due to the great rapidity of

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contraction which results in feeble individual contractions. The great increase in rate of contraction is made possible in part by vagus activity, resulting in a shortening of the refractory phase. It is possible, experimentally, to increase the rate in fibrillation three- or fourfold by vagus stimulation, Samojloff.[6] Hering[7] and Haberlandt[8] suggest that fibrillation is due to rapid stimuli issuing from the A-V node rather than from one or more ectopic foci anywhere in the auricles or ventricles, and Scherf[9] assumes that the sinus node may play a similar rôle.

The foregoing conception that fibrillation is a form of tachysystole or coördinated rapid contraction of the entire chamber is challenged by Garrey[10] on the basis that the excitability is too low and the refractory period, shortened as it may be experimentally, is still too long to permit such rapid coördinated contractions. A more serious objection pointed out by Garrey[10] was that fibrillation stopped in a narrow strip of muscle cut out of a large fibrillating mass even if the strip were left attached at both ends to the main mass of fibrillating tissue. This experiment is a strong argument against fibrillation being a coördinated contraction of an entire chamber. It is particularly contradictory to the assumption that the tachysystole is due to a single activating focus, because slower waves were seen to pass along this bridge of muscle at times in one direction and at other times in a different direction.

In contrast to the foregoing is the widely accepted "circus theory" as developed by Lewis and his coworkers and based on previous work reported by several observers. Mayer,[11] in 1908, excised a ring of tissue from the bell of the large Medusa Cassipeia and by producing temporary block in one region caused a contraction wave to circulate around this ring. Mines,[12] in 1913, cut a ring of muscle from the heart of a tortoise, including auricle and ventricle. He produced a circulating wave in this specimen and noted that a shortened refractory phase and prolonged conduction time were necessary factors in the production of such a circus mechanism. He suggested at that time that such a circus wave may be responsible for paroxysmal tachycardia and fibrillation of the heart. He also demonstrated circus movement in the auricles of large rays and reported having observed such a preparation in which the circulating wave completed about fifty revolutions. Garrey[13] cut a wide ring of tissue from the fibrillating ventricle of a marine loggerhead turtle and observed that this wide ring continued to fibrillate. By cutting this fibrillating ring so as to make it narrower, fibrillation gave way to a circulating movement which Garrey called "circus motion."

The further development of the circus theory of fibrillation was then undertaken by Lewis and his coworkers and they have offered much experimental evidence as proof of the assumption that flutter

and fibrillation are due to a single, rapidly circulating, mother wave giving off centrifugal waves to the remainder of the chambers involved.

Lewis, Feil and Stroud[14] induced experimental auricular flutter in animals and recorded the electrocardiographic phenomena by direct leads from the auricles. They determined that the direction of the excitation wave was independent of the point of electrical stimulation. They traced the course of the excitation wave in flutter and established its path over the surface of the right auricle and the exposed portion of the left. The remainder of the path was calculated.

In a later publication Lewis[15] describes the underlying mechanism as a single circulating central or mother wave which traverses the same path constantly and which sends out centrifugal waves to the auricular musculature not in contact with the mother wave. Impure flutter and auricular fibrillation are stated to be due to the same mechanism, except that the single, central mother wave and centrifugal waves are deviated from the original paths by local areas of block or areas of partial refractory state not yet completely recovered. It is emphasized that there is only one central or mother wave in auricular fibrillation (Lewis[16]) whose location is usually such as to encircle the superior and inferior vena cava, regardless of the point at which the electrical stimulus was applied.

Lewis, Drury and Iliescu[17] studied clinical flutter in man by applying chest leads in three different planes. The rotation of the electrical axis with each auricular cycle was thus calculated and found to be 360° in the three planes, thus apparently substantiating the experimental conclusions previously quoted.

De Boer,[18] working with frogs' hearts, experimented with ventricular fibrillation after bleeding the animals. He, too, believes that the underlying mechanism is a circulating excitation wave passing through the cardiac muscles in stages.

The conception that a single mother circulating wave, usually located about the orifices of the two venae cavae is responsible for auricular fibrillation is open to criticism. Rothberger[5] points out that Lewis actually demonstrated *an almost complete circus path in the auricle of only one animal.* Calculations were substituted in the other experiments for those portions of the path which could not be actually demonstrated. He further points out that the taenia terminalis is not in itself a closed anatomical ring, hence the wave of excitation must leave it and then return to it in order to complete the circuit. The circus path is admittedly not along an anatomically distinct tract nor has block been demonstrated to exist to confine the path to such a ring. This is proved by the fact that centrifugal waves pass from the central mother wave to the rest of the auricular musculature. It is difficult to understand why the mother path should remain so con-

fined to one ring-like area. Areas of partial refractoriness or of block are admitted to exist in the path of the central wave in auricular fibrillation, causing this central wave to assume a sinuous path. But why should the impulse always return to the same point of origin? In the case of clinical flutter where the axis rotation was calculated to be 360° with each auricular cycle an objection may be raised that the electrocardiographic tracings from the chest leads probably included the effects from the centrifugal waves as well as from the comparatively narrow central wave. The results would then represent factors other than those from the narrow single central wave. Our experiments with direct leads, to be described later, showed that impulses other than from the auricle may also be registered.

Experiments performed by Scherf[9] raise further difficulties. This observer produced experimental flutter in dogs and then crushed the site where the central wave usually circulates. Electrocardiograms taken after such crushing of the central circulating wave should produce changes in the electrocardiogram, but no such change occurred in 16 of 17 experiments. It is possible, but not probable, that the path of the central wave was not included in the area crushed, hence the theory of Lewis is not altogether disproved by these experiments.

The explanation of fibrillation as proposed by Garrey[10] differs radically from any of the foregoing theories. This author believes that an impulse spreads in all directions in the auricles but that it may be limited or deflected by local areas of transient or permanent block. Relative differences between excitability and conductivity in an area may act like areas of block. The areas of block may shift in location at times or remain or recur at the same points. Such areas of obstruction would cause the impulse to assume circuitous paths and would act to break up the initial single impulse into several "daughter" impulses, each shuttling and weaving about among the areas of block. An area partly enclosed or protected by block from the stimulus at one instant may respond when an impulse reaches it from another direction or after the block has passed. Such an area may then become a center from which further impulses may shuttle about simultaneously and a circus movement obtains when the impulse happens to return to the point of origin. Such a return is not constant nor is it a fundamental factor in the mechanism, in the sense advocated by Lewis.

Our experiments were planned to test the validity of certain features embodied in the various theories of fibrillation. We have seen that the existence of a single focus or a single mother ring which feeds impulses to the remainder of the auricle are important features of two of the more widely accepted theories. It is true that Rothberger states that one or several foci may be responsible for the tachysystole which

he regards as the mechanism of fibrillations; still he leaves the impression that he leans to the idea that one focus is the more likely cause.[19]

Nearly all authors, including Lewis, believe that the underlying mechanism of auricular and ventricular fibrillation is the same. Our first undertaking was to determine whether one focus or one mother ring is the cause of fibrillation. We began working with ventricular fibrillation in the dog because it was easy to induce and because it was permanent. If it is true that one focus or one mother ring is responsible for the mechanism, then complete separation of the two ventricles should result in disappearance of fibrillation from one chamber or at least in very great modification of the electrocardiogram as it appeared in the control taken before the separation of the ventricles.

RESULTS

Ventricular Fibrillation.—In order to determine this point, dogs were used under morphine-sodium barbitol anesthesia and artificial respiration. The thorax was widely opened in order to expose the heart. The pericardium was opened longitudinally and its margins were fixed to the chest wall on either side to form a cradle on which the exposed heart rested. Two direct leads from nonpolarizable boot electrodes were fastened to each ventricle and control tracings were taken. Ventricular fibrillation was induced by a very short faradic stimulation of the base of the right ventricle and a sufficient length of time, usually about one minute, was allowed to pass in order to be certain that the fibrillation which was grossly apparent was permanent and spontaneous. Control tracings of each ventricle were taken in turn when the fibrillating contractions had visibly reached a more or less constant rate. The ventricles were then very quickly severed from one another along the interventricular septum and in most instances the entire heart, including the auricles, was cut completely across. It was important to work very quickly and to be certain that the two fragments were in the same relative position on the pericardial cradle as before the separation, in order to prevent artefacts due to natural slowing of the fibrillation rate or to change in position of the fragments. Electrograms were then taken of each ventricle in turn, after these foregoing precautions were carried out.

It was apparent on gross inspection that both ventricles continued to fibrillate in about the same manner as before separation. This fibrillation was grossly visible for several minutes. Comparison of the electrograms from both ventricles before and after separation in twelve experiments showed practically no change aside from a slowing in rate (Fig. 1). The results of these experiments lead us to conclude that a single mother ring or a single focus cannot be responsible for the mechanism of ventricular fibrillation in both ventricles. As a

further check, an experiment was performed in which simultaneous electrograms of the two ventricles were recorded (Fig. 2). The persistence of the fibrillation in the separated ventricles is clearly shown, as is the gradual slowing in the two sides.

Auricular Fibrillation.—We then embodied a similar principle in experiments designed to test the possibility that a single mother ring or a single focus is responsible for auricular flutter and fibrillation. Dogs prepared in the same way as before were used. The direct leads

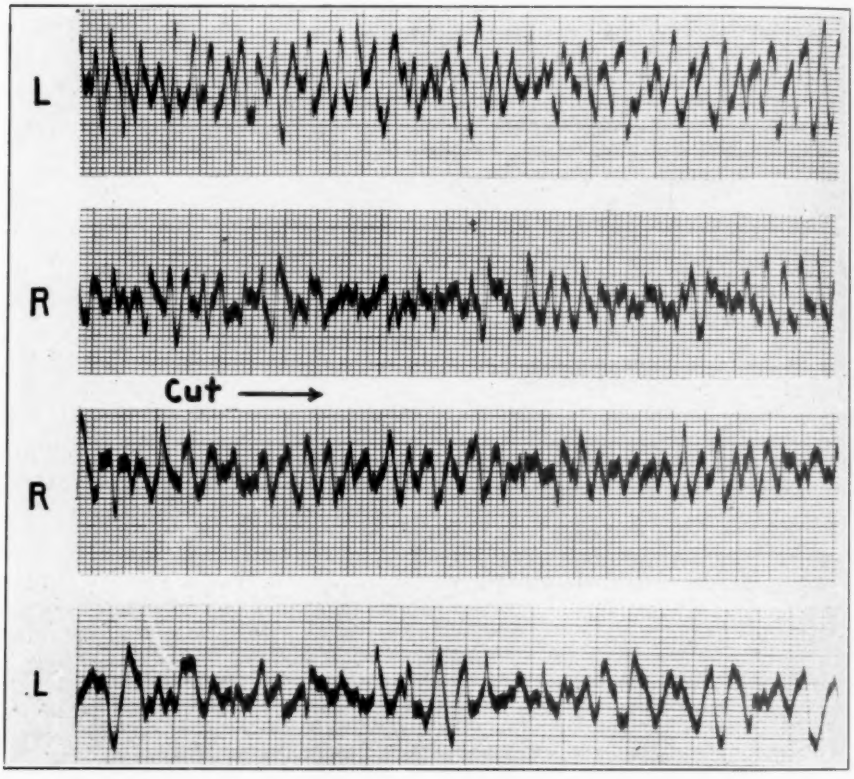

Fig. 1.—Electrograms from right (R) and left (L) ventricles showing persistence of ventricular fibrillation after complete separation of two ventricles by cut. Note in particular the approximate constancy of the two curves of the right ventricle taken before and after the cut.

from the appendices of each auricle were made with nonpolarizable boot electrodes. In the early records one electrocardiograph was used and the records from the auricles were obtained alternately. Later two electrocardiographs were used, each connected with one of the direct leads of an auricle, and simultaneous tracings were taken of both sides. Auricular flutter and fibrillation were induced by short faradic stimulation, of variable frequency and strength, applied to the right auricle, usually just above the inferior vena cava. As is well known, prolonged auricular fibrillation in the dog is not easy to induce. Numer-

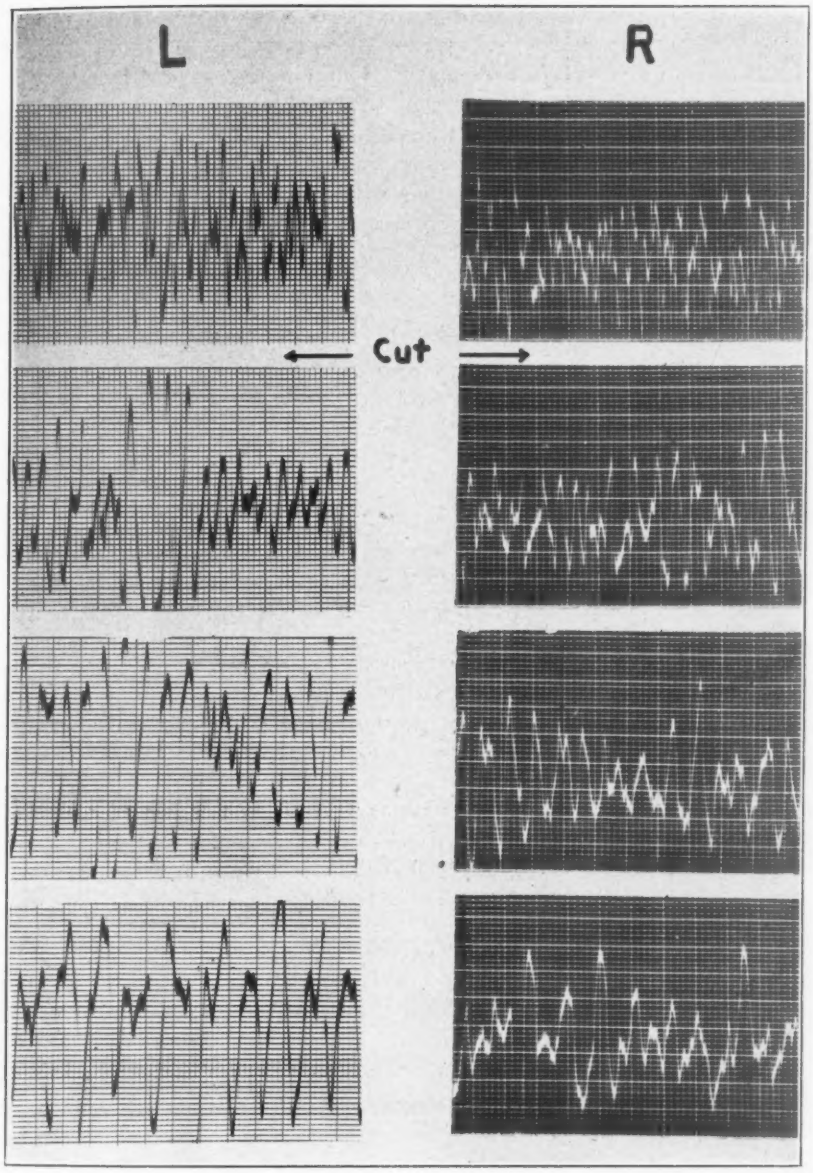

Fig. 2.—Simultaneous electrograms from right (R) and left (L) ventricles showing persistence of ventricular fibrillation after complete separation of two ventricles by cut. Note the simultaneous and progressive slowing of the rate of oscillation in the two ventricles.

ous animals were used and no further manipulations were made until the auricles were visibly fibrillating spontaneously at least twenty-five seconds after the faradic stimulus was removed. A crushing clamp was then applied between both auricles, while fibrillation or flutter still persisted and electrograms were taken from each auricle for some time.

In the early records, such as shown in Fig. 3, the fibrillation of the auricles persisted after the crush, the rate of the *f*-waves being the same as before the crush although their contour is altered slightly. The difference in rate of the *f*-waves on the two sides also persisted after the crush.

Before proceeding with the actual analysis of the later electrograms obtained simultaneously from direct leads from both auricles, it will

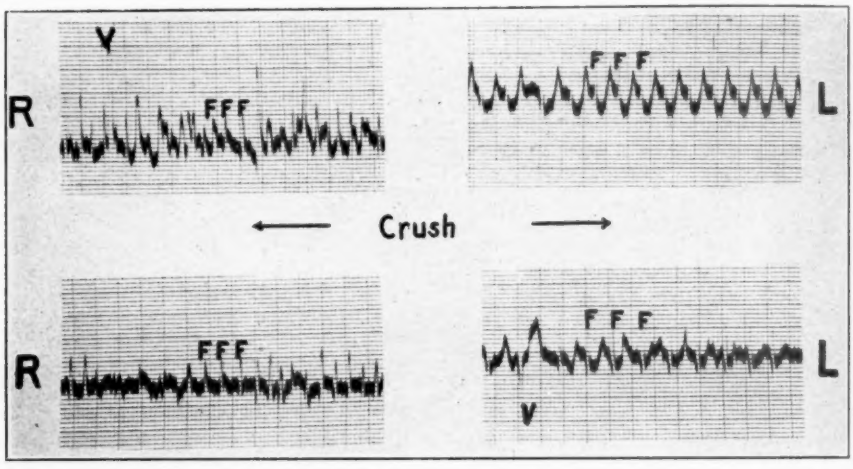

Fig. 3.—Electrograms from right (R) and left (L) auricles showing persistence of impure flutter after complete separation of two auricles by crush. *V*, deflection caused by ventricle; *F*, impure flutter waves. Note the difference in the rate of the flutter waves on the two sides which persists after crush.

be necessary to discuss certain possible artefacts and sources of error due to misinterpretation of the resulting curves.

The first of these is the possibility that the clamp did not reach clear across the auricles. The impulse from the right auricle could then reach the left by pursuing a circuitous course in the auricular tissue extending beyond the tips of the forceps. Such a technical error was prevented by applying the forceps from above toward the ventricles and by examining the position of both blades immediately after clamping and after the experiment was finished. We thus assured ourselves that both blades of the forceps extended not only completely across the interauricular region but also included a large part or all of the ventricles both on the dorsal and ventral aspects of the heart.

There was a further possibility that our crushing forceps were not strong enough to cause complete functional separation of the two

auricles. This was guarded against by using a large, heavy crushing forceps with long blades, such as is used by surgeons to crush bleeding thyroid tissue *en masse*. Examination of the crushed region after removal of the clamps showed distinct tissue destruction, at times resulting in profuse hemorrhage from perforation when the forceps were removed. Gross inspection of the auricles after application of the clamp showed incoördination of rhythm of the two auricles, one chamber beating at a different rate from the other or one auricle continuing to beat while the other was inactive. Electrographic evidence of such dissociation is seen in Fig. 5 in which simultaneous electrograms taken from both auricles shows marked asynchronism and differences in rate.

It was also necessary to consider the possibility that the severe trauma caused by crushing could by itself induce auricular flutter or fibrillation and that the site of injury could then act as a focus from

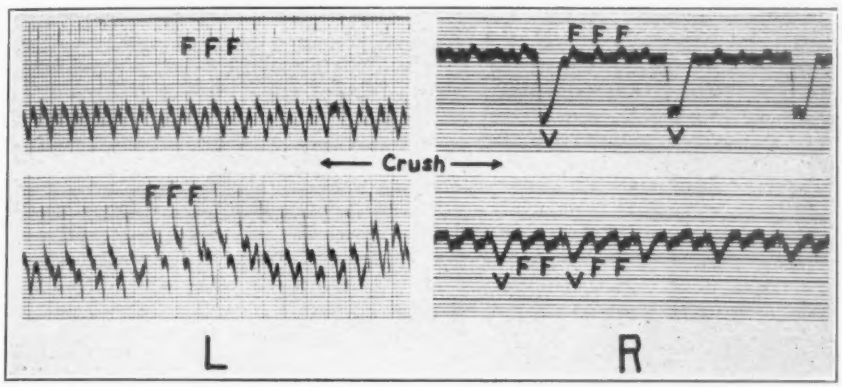

Fig. 4.—Simultaneous electrograms from right (*R*) and left (L) auricles showing persistence of impure flutter after complete separation of two auricles by crush. The string of the electrocardiograph recording the curve from the left is much more sensitive than that from the right.

which impulses could flow to both auricles. We tried many times to produce flutter or fibrillation by clamping and crushing various parts of both auricles during sinus rhythm but were consistently unsuccessful. In fact, all activity, both regular rhythm and fibrillation, would cease if the portion clamped off were small enough. This change was also corroborated electrocardiographically.

In the analysis of the electrograms it was necessary to bear in mind that the various complexes obtained from direct leads to the auricle would differ greatly from the corresponding complexes obtained with indirect leads from the extremities. It was necessary to determine how much the ventricles contributed to the electrograms taken directly from the auricles. Such a precaution is very important as previously pointed out in discussing the work of Lewis, both in the experimental animal and in his calculations in human auricular flutter. Direct leads from each auricle were therefore taken simultaneously with an

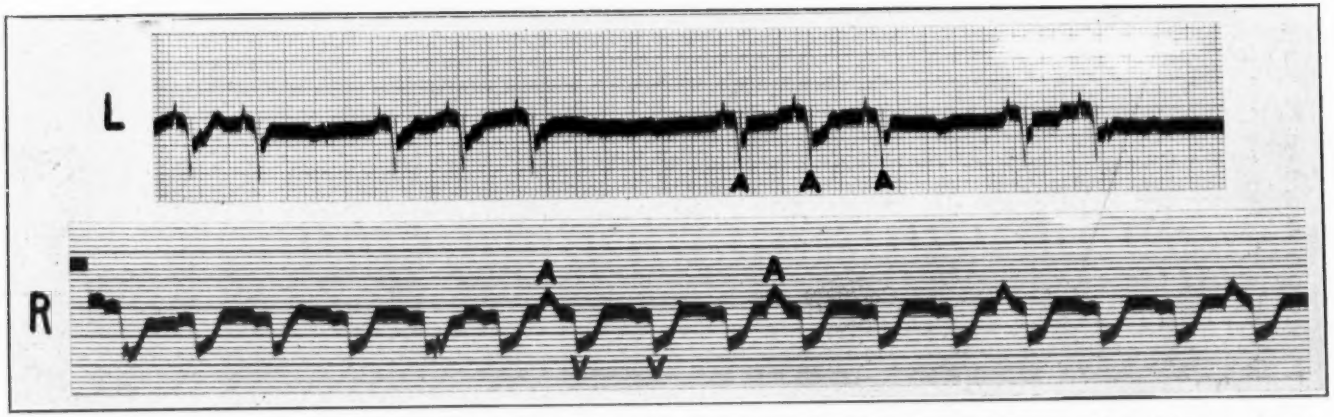

Fig. 5.—Simultaneous electrograms obtained from right (R) and left (L) auricle after complete separation of two auricles by crush and after impure flutter had stopped, showing independent rhythms of the two auricles indicated by oscillations A. *V* is deflection from ventricles.

indirect lead (Lead II). It was found by comparing the curves from such simultaneous direct and indirect leads that the ventricles often produced distinct deflections in the record of the direct leads of the auricles. This was shown when stimulation of the left vagus produced partial A-V block with dropped ventricular complexes, thus clearly separating the ventricular from the auricular complexes.

Heart-block was produced before starting the experiment in order clearly to distinguish the *f*-waves of the induced flutter and fibrillation from components due to the ventricles. For this purpose the region of the bundle of His was crushed. We found that this procedure produced a temporary marked slowing of the ventricle. The ventricular rate then gradually became more rapid. The crush tended to exaggerate the ventricular complexes and make them monophasic so that they were more easily distinguishable.

The curves of Fig. 4 show the simultaneous records of the two auricles in such an experiment after the fibrillation had been induced. In the electrogram from the right auricle (segment on right) the large monophasic ventricular complexes can be recognized; they occur regularly at a rate of 50 per minute. The smaller monophasic *f*-waves occurring at the rate of about 300 per minute can also be readily seen. The electrogram from the left auricle, in which the string was more sensitive than the right, shows no evidence of the ventricular activity. The large deflections are the *f*-waves which correspond in rate to those on the right side.

The lower curves show the simultaneous records obtained after a complete separation of the two auricles by use of the crushing clamp. The ventricular deflections seen in the record on the lower right are smaller and faster in rate, the *f*-waves have not changed in rate but have a different contour probably because of the new injury currents. The contour of the *f*-waves in the left auricle has also been altered for a similar reason.

We are forced to conclude, therefore, that the rapid oscillations in both electrograms, representing *f*-waves of impure auricular flutter, persist after crushing. We came to the same conclusion in seven other experiments conducted in the same manner except that the bundle of His was not always crushed before fibrillation or flutter was induced.

If a single focus or single mother ring, located in an auricle, be responsible for auricular flutter and fibrillation in the intact heart, then functional separation of the two auricles should result in cessation of this condition in the auricle which is not the site of this impulse formation. Such a functional separation, if complete, as it was in our experiments, should prevent the propagation of impulses from the focus in one auricle to the other. Such was not the case. Flutter

and fibrillation continued at about the same rate in both auricles after such functional separation and the *f*-waves derived by direct leads from both auricles simultaneously were only slightly changed in rate.

It is a remote possibility that the mother ring or single focus was sufficiently extensive so that the crush halved it with consequent small effect. It is difficult to conceive that the ring or focus should always be in the same place, namely, where the auricles were crushed. This is especially unlikely as the crushing forceps were not always applied exactly in the same place or plane. Nor would this explain the slight change in rate of the *f*-waves after crushing. Destruction or modification of the ring or focus should result in a greatly altered electrogram. We have already given our reasons for believing that the trauma from crushing did not, in itself, induce flutter or fibrillation in one or both auricles.

CONCLUSION

The conclusion is forced upon us that more than one center or ring must be responsible for auricular flutter or fibrillation. Whether such centers are multiple from the beginning or whether they result from breaking up of an initial impulse into several daughter impulses which shuttle and weave about in both auricles cannot be determined from these experiments. Our experiments do, however, exclude the possibility that only one focus or a single mother ring is responsible for the maintenance of these conditions in the intact heart.

The experiments with ventricular fibrillation are even more convincing because the ventricles were completely separated from one another by cutting. In some instances the entire heart, including the auricles, was cut across along the interventricular septum thus excluding any possibility that impulses were being conducted from one separated ventricle to the other by way of cardiac tissue. The electrograms from each ventricle after such separation were practically the same as before in every experiment. The two halves of the heart could be seen on gross inspection to fibrillate after cutting. The only change to develop was a gradual slowing in each side but this occurred at about the same rate as when the heart was not cut. These experiments are incompatible with the view that ventricular fibrillation in the intact heart is due to a single focus or ring acting as a source for the fibrillary movement.

While our experiments clearly show that a single focus or mother ring cannot possibly be the cause of flutter or fibrillation of the heart and that our results are compatible with the idea that several foci are at work, it must not be construed that our work proves the correctness of the latter view. On the contrary, we feel that much work remains to be done in order to explain the actual fundamental mechanism responsible for this condition.

RÉSUMÉ

1. The various theories which have been offered to explain flutter and fibrillation of the heart and the arguments *pro* and *con* for each are presented.

2. A series of experiments were designed to test the validity of the various theories. Flutter and fibrillation was induced in the auricles in one series and ventricular fibrillation in another. Control electrograms with direct leads, using nonpolarizable boot electrodes, were recorded from both auricles or from both ventricles. In most cases the records were taken simultaneously. Complete functional or actual separation of one auricle or ventricle from the other was then performed and the electrograms from each were again recorded. The curves show definitely that flutter or fibrillation still continues in each separated chamber. Comparison of the electrograms before and after such separation shows very little change in the rate of the *f*-waves.

3. Such results are obviously incompatible with any theory that flutter or fibrillation in the heart is due to a single focus or a single circus ring sending centrifugal waves into the other auricle.

4. Our experiments are not incompatible with the theory that the impulse becomes broken up into several daughter rings or waves which shuttle and weave about the myocardium. Nor are our results incompatible with the conception that multiple foci may be responsible. It is emphasized, however, that we offer no proof of the correctness of either of these views. On the contrary, we feel that further work is necessary in this direction.

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CONGENITAL HEART DISEASE

A Clinical and Pathological Study of Two Cases of Truncus Solitarius Aorticus (Pulmonary Atresia)*

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CONGENITALLY anomalous hearts with a single arterial trunk are not common. These anomalies can be divided into the following groups: (1) true persistent truncus arteriosus; (2) truncus solitarius pulmonalis; (3) truncus solitarius aorticus.

The first group, *persistent truncus arteriosus*, is the least frequent of the three. Feller,[1] in a critical review of the cases reported as truncus communis, could find only a few authentic instances. This abnormality is due to the persistence of the primitive arterial trunk which remains undivided. Here one should expect four cusps to be present. Cases with a persistence of four well-formed semilunar cusps are extremely rare (Abbott,[2] Feller[1]). By means of localization of the ostiae of the coronary arteries and the finding of evidences of fusion of two cusps, Feller was able to determine the previous presence of the four valve cusps in those cases of true persistent truncus in his series where apparently only three were present. The presence of four well-formed cusps associated with a single arterial trunk is usually positive proof of an undivided primitive arterial trunk (Abbott[2]). Nevertheless one occasionally observes instances of a persistent truncus arteriosus with only three semilunar cusps (Abbott[3]).

More frequently, however, one finds that many of the cases wrongly reported as true persistent truncus arteriosus, are in reality cases in which there has been a complete division between the aorta and pulmonary artery, a truncus solitarius aorticus or pulmonalis existing. Due to some congenital malposition of the aortic septum one of the vessels is narrowed and fails to grow normally. This vessel, if obliterated at its orifice, may undergo a complete atresia so that one usually finds a small remnant of the original vessel or even an atresic cord (Abbott[2]). The remaining vessel, aorta or pulmonary artery, dilates.

Atresia of the aorta is much less frequent than that of the pulmonary artery (Abbott,[2] Shapiro[4]). In the cases of atresia of the aorta (*truncus solitarius pulmonalis*) the pulmonary artery enlarges and the sinuses of Valsalva of the enlarged pulmonary artery are free of coronary arteries. The coronary arteries arise from the aortic arch or vestige of the aorta. A complete description and review of the litera-

*From the Laboratories of the Mount Sinai Hospital, New York City. Aided by a grant from the Lucius N. Littauer Foundation.

ture of this anomaly can be found in the classical monograph of Abbott and also in a recent paper by Shapiro.

The third group, *truncus solitarius aorticus*, which is due to an atresia of the pulmonary artery, is the most frequent of the three. The aorta dilates while the pulmonary artery undergoes progressive atresia. The pulmonary circulation is usually maintained through a widely patent ductus arteriosus, or in some instances, via branches directly from the aorta. This anomaly has been reported by many observers (Mönckberg,[5] Dickson and Fraser,[6] Wheeler and Abbott,[7, 8, 9] and others). Abbott collected 31 cases of this congenital abnormality. Two more cases of atresia of the pulmonary artery recently observed at the Mount Sinai Hospital are added to this group because of the unusual associated anomalies present.

CASE REPORTS

CASE I.—Congenital atresia of the orifice of the pulmonary artery, with closed interventricular septum, absence of tricuspid valve, aplasia and aneurysmal dilatation of the the right ventricle, patent foramen ovale and patent ductus arteriosus; truncus aorticus solitarius; single coronary artery; neuroblastoma of adrenal gland with metastases to the liver.

CLINICAL HISTORY

R. G., aged six months. Admitted January 19, 1931. Died January 22, 1931.

Chief Complaint: Infection of vulva of one week's duration.

Family History: Father and mother well.

Past History: Full term baby, weighed seven pounds, three ounces at birth. The child had never been ill except for the fact that the cyanosis and dyspnea which were noted at birth had become definitely increased in the last two months.

Physical Examination: Well-developed female child who appeared markedly cyanosed. The breathing was rapid. The head appeared small, measuring 40 cm. The chest was round and rather prominent. Both sides were symmetrical. There was definite cyanosis and clubbing of both fingers and toes. The heart was enlarged to percussion both to right and left. There was a marked rough systolic murmur heard best over the second interspace on the left side transmitted toward the apex. The rate was rapid and the rhythm regular. Dr. S. Karelitz noted that the systolic murmur had a peculiar resonant quality, almost like that heard in an aneurysm. It was his impression at that time that there was a congenital heart disease with pulmonic stenosis, tremendous enlargement, especially of the right heart, and most likely other cardiac anomalies. The liver was palpable one and a half fingerbreadths below the costal margin. The child remained in the hospital for three days and succumbed to an erysipelas of the vulva.

Blood count:—

R.B.C.	5,300,000	
W.B.C.	15,000	
Polymorphonuclears	52	per cent
Monocytes	3	per cent
Lymphocytes	45	per cent

Roentgen Examination: January 20, 1931 (M. L. Sussman, M.D.): Examination of the chest showed no abnormality in the lungs. The heart was markedly en-

larged. The enlargement was general but particularly upward and to the right, in which region it assumed a globular appearance, the upper margin of the cardiac shadow reaching well up to the second rib posteriorly. The cardiophrenic angle on this side was perfectly clear. On the left side the cardiac contour appeared to consist of two curves, the point of union being suggestive of the junction of two chambers. (Fig. 1.)

The findings were extremely atypical, the enlargement upward and to the right being of the appearance often seen with extreme enlargement of the left auricle. The general configuration, however, was very strongly suggestive of a congenital heart lesion. Heart measurements were: Ml 4.3; Mr 5.7; T 10.0; Chest 14 cm. Film taken at 40 inches.

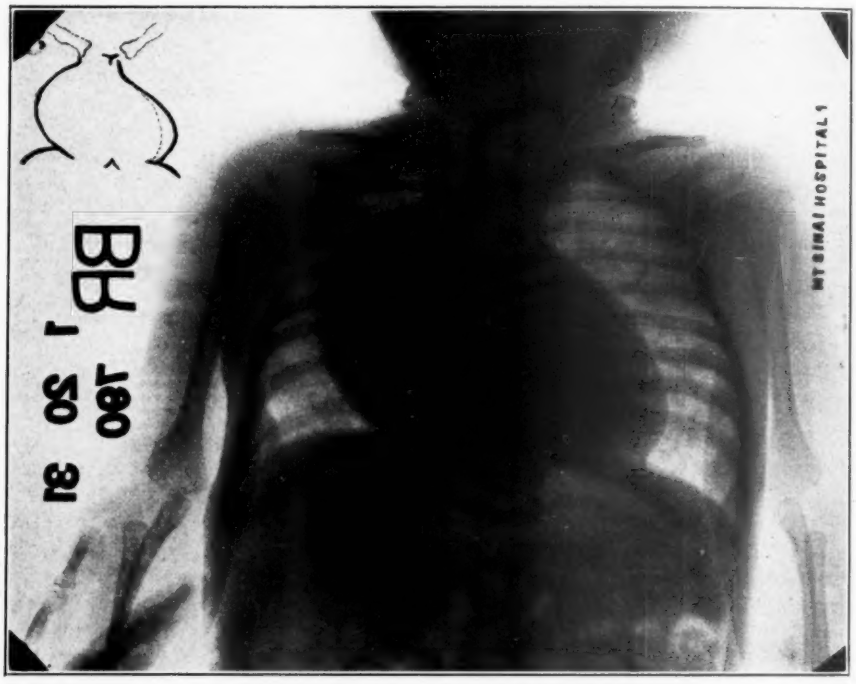

Fig. 1.—Roentgen ray appearance of chest. (Case I.)

Autopsy (Performed by Dr. P. Klemperer).—The body was that of a six months' infant, well developed, well nourished and in incomplete rigor mortis. There was a mottled purplish area of discoloration about the size of a twenty-five cent piece on the right side of the vulva.

Lungs: Grossly normal.

Heart: The heart* presented externally a very unusual appearance. The region usually occupied by the right ventricle was totally collapsed and gave the appearance of a cyst which was separated from a smaller multilocular cyst. The latter formed the apex of the right ventricle and had several communications with the main cavity of the right ventricle (Fig. 2).

The heart measured 4.5 cm. in diameter at its base. The pericardium was smooth and glistening. At the base of the heart there was only one large vessel

*The specimens were paraffinized by the method described by Gross and Leslie.[10] This facilitated the study of the specimens.

which seemed to arise from the left ventricle. The right auricle was unusually large. Its cavity was about the size of the dilated right ventricle. The wall of the right auricle was hypertrophied, measuring 0.2 cm. The musculi pectinati were well developed. The superior and inferior venae cavae entered the right auricle in their usual position. Instead of the tricuspid leaflets one found only a sharp ridge at the site of the auriculo-ventricular sulcus in its internal aspect. The tricuspid valve, chordae tendineae, and papillary muscles were completely lacking. The cyst seen externally was in reality a dilated right ventricle whose wall was extremely thin, measuring roughly 0.05 cm.

In attempting to trace the circulation from the right ventricle upward, it was found that there was no opening from the ventricle either into a pulmonary artery or aorta and that there was no defect anywhere along the interventricular septum (Fig. 3). The foramen ovale, however, was widely patent.

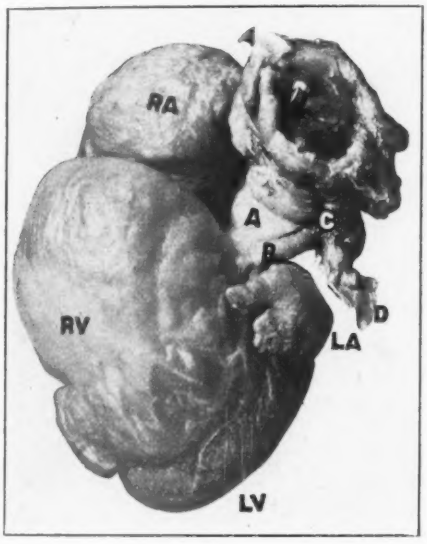

Fig. 2-*A*.

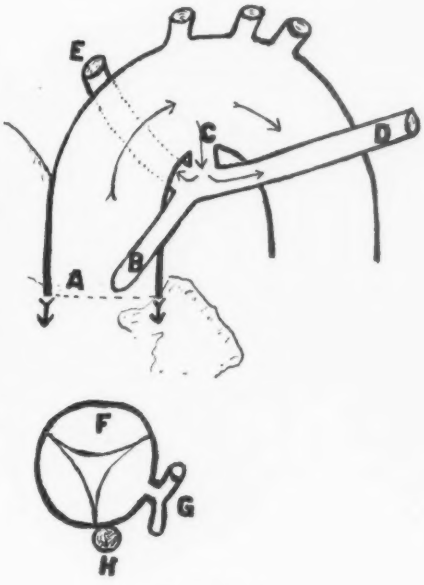

Fig. 2-*B*.

Fig. 2, A and B. Photograph of paraffinized heart, with diagram showing relationship of aorta to pulmonary artery. Key to Fig. 2, A and B: *A*, aorta; *B*, atresic pulmonary artery; *C*, patent ductus arteriosus; *D*, left pulmonary artery; *E*, right pulmonary artery; *F*, cross section of aorta near origin; *G*, single coronary artery; *H*, cross section of atresic pulmonary artery near origin; *R.A.*, right auricle; *L.A.*, left auricle; *L.V.*, left ventricle; *R.V.*, right ventricle.

The left auricle was very small in size, the transverse diameter of its cavity being less than one centimeter as compared to 3.25 cm. of the right. The left auricle received pulmonary veins from both lungs. The mitral ring was small but the mitral cusps, chordae tendineae, and papillary muscles were well developed. The wall of the left ventricle, as well as that of the interventricular septum measured 0.4 cm. in thickness. Arising in its usual position from the left ventricle there was one large vessel (aorta) with three cusps: one right anterior, one left anterior, and one posterior. A coronary artery arose in the sinus of the cusp situated to the left (Fig. 2-*B*). This coronary vessel seemed to be the only artery supplying the heart. At the under surface of the arch the aorta gave off one vessel (patent ductus arteriosus) which branched three ways, one branch going to the left lung,

another branch going posteriorly to the right lung, and a third branch coursing downward and terminating anteriorly to the right of the aorta at its base. On cross section this vessel was the pulmonary artery which had undergone atresia with a complete obliteration at its base. Arising in the usual fashion from the arch of the aorta were the innominate, left common carotid, and subclavian arteries.

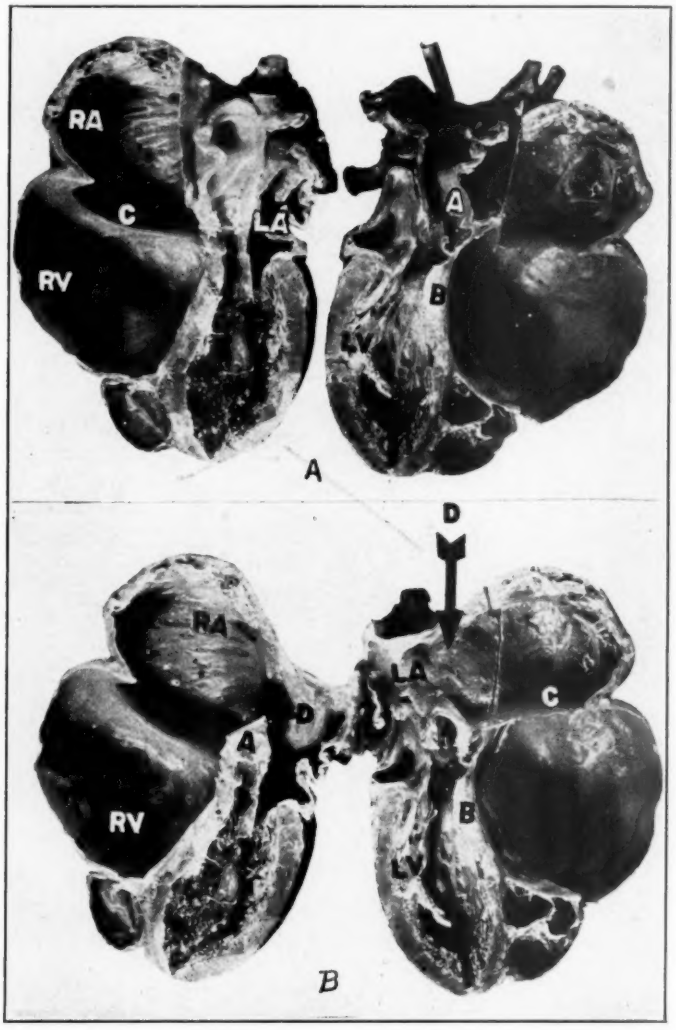

Fig. 3-*A*.—Photograph of sagittal section of anterior portion of heart, showing single arterial trunk, the auricular and ventricular cavities, as well as closed interventricular septum.

Fig. 3-*B*.—Photograph of sagittal section of the posterior portion of heart with widely patent foramen ovale. Key to Fig. 3, A and B: *A*, aorta; *B*, closed interventricular septum; *C*, tricuspid valve; *D*, widely patent foramen ovale; *R.A.*, right auricle; *L.A.*, left auricle; *L.V.*, left ventricle; *R.V.*, right ventricle.

The course of circulation in this heart was, therefore, from the right auricle through the auricular septal defect into the left auricle downward into the left ventricle. From there on, the mixed blood of the right and the left hearts passed into the aorta, part going into the systemic circulation, part passing through the

patent ductus arteriosus into both pulmonary arteries supplying the lungs. The right auricle and left ventricle apparently carried on the main burden of the circulation. The right ventricle was a blind pocket.

MICROSCOPICAL SECTIONS

Heart.—Left Ventricle and Right Auricle.—The muscle fibers were well formed, and the nuclei were prominent. There was no evidence of scarring or inflammation. The coronary arteries and branches were normal.

Auriculo-ventricular Sulcus (Right).—A section taken through the ridge where the tricuspid valves normally arise showed a thickened fibrous layer arising at the point where the right auricle meets the right ventricle. The fibrous layer projects for a short distance where it was covered by the endocardium. There were no evidences of inflammation. In the pericardium of the auriculo-ventricular sulcus a large coronary artery was seen.

Right Ventricle.—The musculature of the right ventricle was compressed between a thickened and elasticized endocardium and the thickened fibrous visceral pericardium. The greater portion of the wall of the right ventricle was fibrous and elasticized, with little or no musculature present.

Adrenal Gland.—Examination of the left adrenal gland revealed that it was enlarged to the size of a walnut and measured 3.5 by 3.0 by 3.5 cm. The medial border of the tumor-like enlargement of the gland presented a thin margin of normal appearing adrenal tissue. Section of the gland revealed a walnut-sized tumor mass occupying the entire medullary space. It presented a mottled grayish-pink and dark red color, rather firm in consistency with a few yellow areas (possibly necrotic tissue). The medial edge, as has been stated, was composed of normal appearing adrenal tissue, especially cortex. The cortical tissue entirely surrounded the tumor but in the distal portions was very much thinned out, appearing like a ball surrounded by a cover with a dense accumulation of the covering at one end. The right adrenal gland presented no abnormal findings. Weight, 20 grams.

Liver.—The liver was somewhat enlarged, especially the right lobe. On the surface of the liver a few small pearly grayish-pink depressed areas, varying in size from 2 to 8 mm. could be seen. Cross section revealed a number of these nodules scattered in the liver parenchyma, a few being superficial. The right lobe presented a diffusely fatty appearance, parboiled, and glassy. The left lobe of the liver also showed a few metastatic nodules but the liver parenchyma was dark red and the normal architecture was very indistinct because of the marked congestion. The hepatic artery, portal vein, and hepatic veins were negative. The gall bladder and bile ducts presented no abnormal findings.

Kidneys.—The left kidney showed normal fetal markings. Cut section revealed only congested parenchyma. The renal artery and vein showed no abnormalities. The superior surface of the kidney had been flattened by the left adrenal tumor mass. The right kidney was found at the brim of the pelvis anterior to the aorta. A single right renal artery could not be found. Main branches from both the right and left common iliac artery were seen entering the kidney, that from the right entered the anterior surface of the kidney after coursing down the posterior surface and entering the hilus which was on the lateral border of the kidney. The branch from the left common iliac artery entered directly into the renal substance on its posterior surface in its midportion. The right ureter entered the kidney on the lateral surface somewhat anteriorly and in front of the branch of the right common iliac artery. Except for its anomalous arterial circulation, the kidney appeared normal both on its surface and on cross section. The right renal vein came from the hilus to enter the inferior vena cava at a somewhat lower level.

Diagnosis.—(1) Congenital malformation of the heart; (2) atresia of the pulmonary artery at its mouth without interventricular septal defect; (3) aplasia and marked dilatation of the right ventricle; (4) patent foramen ovale; (5) absence of tricuspid valve and its chordae tendineae and papillary muscles; (6) truncus solitarius aorticus; (7) patent ductus arteriosus; (8) single coronary artery.

Neuroblastoma (left adrenal gland) with metastases to liver; chronic passive congestion of liver, spleen, and kidneys; degeneration of liver, and erysipelas of right vulva (clinically).

CASE II. Congenital atresia of the orifice of the pulmonary artery, truncus aorticus solitarius (patent ductus arteriosus), interventricular septal defect. Single coronary artery.

CLINICAL HISTORY

L. S., aged three months. First Admission: February 28, 1930. Dismissed: June 9, 1930.

Chief Complaint: Cough and fever.

Family History: Entirely negative.

Past History: Child of three months, with a history of cyanosis since birth. Both history and development of the child were normal.

Physical Examination: The outstanding feature was cyanosis of the lips and extremities, which was marked when the child cried or strained. There was distinct clubbing of the fingers. There was no dyspnea or edema. The liver was felt one finger below the costal margin. Examination of the chest showed dullness in the R. U. L. with some higher pitched breathing but no râles. The cyanosis was thought to be due to a congenital cardiac lesion and an atelectasis of the lungs. The heart did not appear enlarged on percussion. It was regular and no murmurs were heard.

Blood:	
Hgb	88 per cent
R.B.C.	5,600,000
W.B.C.	8,700
Polymorphonuclears	46 per cent
Lymphocytes	44 per cent
Monocytes	6 per cent
Eosinophiles	2 per cent
Basophiles	2 per cent

Wassermanns of mother, father, and child were negative.

Second Admission: January 26, 1931. Died: January 27, 1931.

The child was perfectly well until three days before its second admission (at the age of ten months) when it developed cough, fever, dyspnea, and increased cyanosis, and succumbed the following day to a bronchopneumonia.

X-ray examination and fluoroscopy, as well as physical examination confirmed the impression that one was dealing with a congenital heart condition.

Autopsy (Performed by Dr. P. Klemperer).—Body was that of a well-developed infant with marked cyanosis and clubbing of finger tips.

Abdomen: Situs viscerum normal. No ascites present.

Thorax: There was a moderate beading of ribs. A section of a costochondral junction showed irregular line of bone formation extending into the cartilage with a widened zone of ossification. The pleural cavities were free. The lungs externally showed congestion of R. U. L. and R. L. L., with increased firmness of texture.

Heart: The heart was globular and its apex was made up of the left ventricle. The pericardium was smooth and glistening. Externally, there seemed to be only

one large vessel at the base of the heart. The width of the heart at the base was 4 cm.; from the base to the apex the heart measured 4.5 cm. (Fig. 4.)

On sagittal section the heart had four chambers. The right auricle received the superior and inferior venae cavae in the usual sites. The right auricle and tricuspid valve presented no abnormalities. The right ventricular cavity was smaller than the left. The wall thickness measured 0.4 cm. There was a defect 0.5 cm. in diameter in the intraventricular septum at its anterior superior aspect just below the origin of the aorta (Fig. 5-*A* and *B*). The left auricle was smaller than the right and received pulmonary veins from both lungs. The interauricular septum was completely closed. The mitral valve, chordae tendineae, and papillary muscles were well developed. The musculature of the left ventricle was compact. The wall measured 0.4 cm.

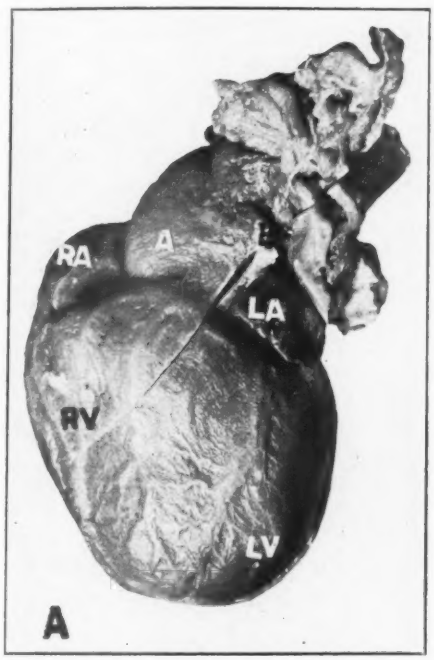

Fig. 4-*A*.

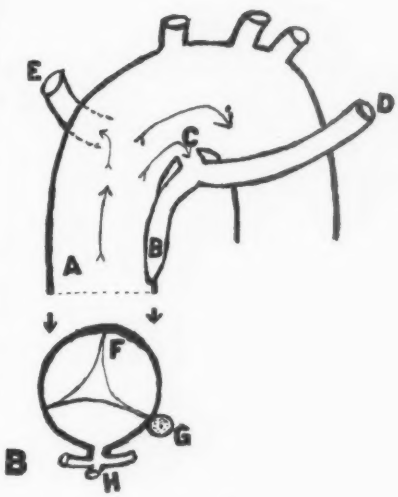

Fig. 4-*B*.

Fig. 4, A and B.—Photograph of paraffinized heart (anterior view) with diagram showing the relationship between aorta and pulmonary artery. Key to Fig. 4, A and B: *A*, aorta; *B*, atresic pulmonary artery; *C*, patent ductus arteriosus; *D*, left pulmonary artery; *E*, right pulmonary artery; *F*, cross section of aorta near origin; *G*, cross section of atresic pulmonary artery near origin; *H*, single coronary artery; *R.A.*, right auricle; *L.A.*, left auricle; *L.V.*, left ventricle; *R.V.*, right ventricle.

Riding above and to the right of the interventricular septal defect was the large aortic trunk which had three cusps, one anterior and two posterior of equal size (Fig. 4-*B*). From the sinus of Valsalva of the anterior cusp was a large opening for the coronary artery. This was the only coronary artery that could be found arising from any of the vessels in or near the heart. This coronary vessel, therefore, seemed to be the sole arterial supply to the heart. On the under surface of the aorta near the arch there arose one small branch which went directly to the right lung. On the left side there was another branch (patent ductus arteriosus) which, shortly after leaving the aorta, gave rise to one vessel going upward and backward to the left lung and another vessel which coursed downward and terminated

to the left of the aorta about 1 cm. from its base. On cross section, this latter vessel (atresic pulmonary artery) was seen to end in a blind pocket, with a few puckerings at its base suggestive of regressed or incompletely formed valves.

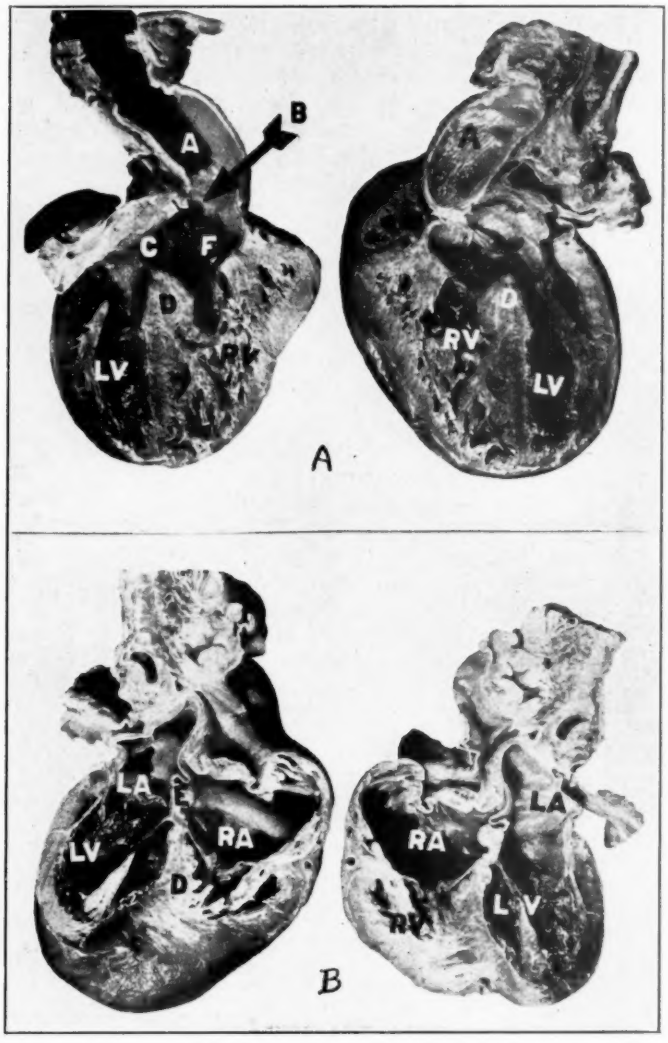

Fig. 5-A.—Photograph of sagittal section of anterior portion of heart showing single arterial trunk overriding an interventricular septal defect. Note single coronary orifice.

Fig. 5-B.—Photograph of sagittal section of posterior portion of heart, showing closed interauricular septum. Key to Fig. 5, A and B: *A*, aorta; *B*, orifice of single coronary artery; *C*, interventricular septal defect; *D*, interventricular septum; *E*, interauricular septum; *F*, aortic valve cusps; *L.A.*, left auricle; *R.A.*, right auricle; *L.V.*, left ventricle; *R.V.*, right ventricle.

The truncus showed evidence of incomplete rotation, in that the right coronary artery came off anteriorly* and the termination of the atresic portion of the pulmonary artery was situated more to the left.

*Considered anatomically with reference to the heart and not with reference to the body.

The innominate arteries, the left common carotid artery, and the left subclavian artery arose from the arch of the aorta, in their usual position.

Heart.—(Microscopical sections.) Sections through myocardium showed no evidences of inflammation, or other pathological changes.

Inferior Vena Cava.—Negative.

Liver.—Somewhat enlarged. The lower margin was thin. The surface was normal. Section revealed marked loss of lobular markings, yellowish color and parboiled appearance of parenchyma. The portal vein, hepatic artery, gall bladder, and bile ducts were all normal.

Spleen.—Distinctly enlarged, firm, dark. The cut surface showed congestion with distinct enlargement of follicles, and did not scrape. A small accessory spleen was seen in the hilus. The splenic vein was normal.

Kidneys.—Fetal lobulations were distinct. The cut section revealed moderate congestion. The right renal artery was double immediately after its origin in the aorta. The left was normal. Ureters and bladder were normal. The urethra was long but free of anomaly.

Adrenal Glands.—Normal in size.

Thymus.—Not excessively enlarged.

Gastrointestinal Tract.—The esophagus and stomach were normal. The small intestine showed marked hyperplasia of lymphoid tissue throughout, including Peyer's patches and solitary follicles. The large intestine was essentially similar.

Diagnosis.—(1) Congenital malformation of the heart; (2) atresia of the pulmonary artery; (3) truncus aorticus solitarius; (4) patent ductus arteriosus; (5) subaortic interventricular septal defect; (6) single coronary artery.

Bronchopneumonia R. U. L. and R. L. L.; acute bronchitis; chronic passive congestion of liver, spleen, kidneys, gastrointestinal tract, and pancreas; degeneration of liver; follicular hyperplasia of small and large intestines and spleen; mild rickets; and accessory spleen.

SUMMARY

Atresia of the pulmonary artery is a relatively uncommon condition. In the cases with a defect in the interventricular septum, the average duration of life is three and four-tenths years according to the statistics collected by Abbott[2] in a review of 24 cases. The maximum age reached was thirteen years. In our Case 2 the child lived up to ten months. Its death was hastened by a mild bronchitis and bronchopneumonia.

This anomaly is far more serious when associated with a closed interventricular septum. Of the 7 cases collected by Abbott, the average duration of life was twelve weeks, with a maximum age period of six months. Our Case 1 lived six months with symptoms of progressive heart failure and increasing cyanosis and dyspnea, finally succumbing to an erysipelas.

Clinically, both children were cyanotic at birth. When admitted to the hospital, cyanosis, distinct clubbing of the fingers, and enlargement of the liver were noted. These symptoms were, however, more intense in Case 1, with the intact interventricular septum. Here, also, the diagnosis of a congenital cardiac defect was aided by the extreme enlargement of the organ and by the presence of a rough systolic

murmur with a peculiar resonant quality suggestve of an aneurysm, heard best over the second interspace on the left side and transmitted to the apex. The x-ray film of the heart presented an unusual appearance, that of a large egg occupying almost the entire chest wall (Fig. 1). The correlation of the x-ray findings with the post-mortem findings showed the enlargement to be due to the aneurysm of the right ventricle and the dilated and hypertrophied right auricle. It was also possible to distinguish both ventricles on the x-ray plate.

In the case with the defect in the interventricular septum no enlargement of the heart was noted, neither were there any murmurs heard. Zimmerman[11] recently reported a case of truncus arteriosus communis with an interventricular septal defect in a colored male of twenty-five years, the cause of whose death was an automobile accident. Considered from the point of view of mechanics of circulation, Zimmerman's case is similar to our second case in which the baby lived to the age of ten months. A case reported by Wheeler and Abbott[7] of pulmonary atresia and other cardiac anomalies survived until the age of twenty-nine.

The absence of one coronary in both cases is an unusual anomaly which is extremely rare in otherwise normal hearts. It is well known that one coronary artery can be an adequate source of blood supply to maintain intracardiac circulation, provided there are sufficient anastomoses.[12] This fact is well demonstrated by Case 2 in which both ventricles were well developed. Microscopical examination of the myocardium showed no evidences of degeneration or scarring.

The case with the closed interventricular septum and marked dilatation of the aplastic right ventricle with aplasia of the tricuspid valves is puzzling. The most obvious explanation as to the cause of the aplasia and dilatation of the right ventricle is a nutritional disturbance and the increased intraventricular pressure necessary to force blood into the left side of the heart.

It is also possible that in this case the pulmonary artery was originally patent though incompletely developed. The right coronary artery may have had an abnormal origin from this vessel. With increasing stenosis of the pulmonary artery two phenomena arose: namely, the right coronary supply became insufficient and the right ventricle had to overcome the pressure of the left heart in order to force blood through the foramen ovale. Possibly both of these factors led to the final aplasia and dilatation of the right ventricle.

While it is impossible to find traces of this hypothetical right coronary artery in this case, it is to be noted that a case of aplasia of the right ventricle occurring with atresia of the pulmonary artery and closed interventricular septum described by Abbott apparently possessed two coronary arteries arising from the aorta and, secondly, cases with abnormal origin of one coronary artery from the pulmonary

artery described by Abrikossoff,[13] Heitzmann,[14] Krumbhaar,[15] Schley[16] and Scholte[17] showed evidences of myocardial degeneration and extensive fibrosis in the areas supplied by the misplaced coronary artery.

In the case described by Abrikossoff, aneurysmal dilatation of the left ventricle was associated with a misplaced coronary artery arising from the pulmonary artery.

The association of cardiac anomalies with abnormalities elsewhere in the body has been frequently emphasized. Other anomalies were present in both of our cases. Of special interest, however, was the presence of a neuroblastoma of the adrenal gland with metastases to the liver in Case 1, a child of *six months*.

The author is indebted to Dr. Louis Gross and Dr. Maude E. Abbott for their advice and criticism, to Dr. Bela Schick for the use of clinical material, and to Dr. Leopold Jaches for the use of the x-ray material.

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Department of Clinical Reports

PROLONGED PAROXYSMAL TACHYCARDIA

Case Report*

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CASE REPORT

M. B., cobbler, aged fifty years, an Armenian, entered the Second Medical Service of the Boston City Hospital on September 22, 1930. The history was obtained with difficulty because the patient spoke very little English. He had been in good health and had worked continuously until two weeks before entrance. At this time, following a heavy meal, the patient was seized with cramp-like pains in the umbilical region, later rising to the epigastric region. The pain fluctuated in severity, but persisted.

At entrance, the physical examination was unimportant, except that the pulse rate was 180 per minute. The rhythm was regular. The blood pressure was 95/85 millimeters of mercury. The respirations were 28 per minute. A few crepitant râles were heard at both bases posteriorly. Slight tenderness was elicited in the epigastrium. An electrocardiogram taken September 22 showed paroxysmal tachycardia, probably auricular in origin. The rate was 200 per minute.

Though it was believed that the patient had had a coronary occlusion, no evidence appeared to support this suspicion. There was no fever. The white blood cell count at entrance was 10,500 per cubic millimeter of blood. Later, it fell to 4,000 per cubic millimeter of blood. The paroxysmal tachycardia persisted for thirty-five days. The only change in his condition throughout the thirty-five days was gradually increasing congestive failure until the liver was definitely engorged and slightly tender; the râles at the lung bases increased, and a small amount of demonstrable fluid appeared at both bases. Curiously, there was more on the left than on the right.

During the thirty-five days, he received the following medication: quinidine sulphate, 30 grains each day for two days, was given first, without effect on the heart. This was stopped because of nausea and vomiting. Two doses of digalen were given intravenously. The first dose was 9 grains. The second dose, given twenty-four hours later, was 10 grains. There was no appreciable effect. The following day powdered digitalis, 9 grains, was given by mouth. This dose was repeated each day for three days. The dose was then reduced to 4½ grains daily. This was continued for eleven days. The dose was then reduced to 1½ grains daily. Throughout this time, the patient was under close observation. His heart rate was counted every hour throughout the twenty-four hours. There was no appreciable effect from the digitalis. The digitalis was discontinued three days

*From the Thorndike Memorial Laboratory and the Second and Fourth Medical Services (Harvard) of the Boston City Hospital.

before the paroxysm ceased. Quinidine sulphate, 6 grains in one dose, was given intravenously fourteen days after admission, two days after the dose of digitalis had been reduced to 4½ grains daily. The cardiac rate dropped from 180 per minute to 150 per minute in five minutes and then returned to 180 per minute gradually in twenty minutes. Forty-eight hours before the paroxysm ceased, quinine hydrochloride was given by mouth in 10-grain doses. An electrocardiogram taken after the first two or three doses showed a rate of 176 per minute, which was slightly lower than the average rate. After he had had a total of 70 grains of quinine hydrochloride over a period of forty-eight hours, his heart suddenly resumed a normal rhythm with a rate of 80 per minute. There was immediate improvement in

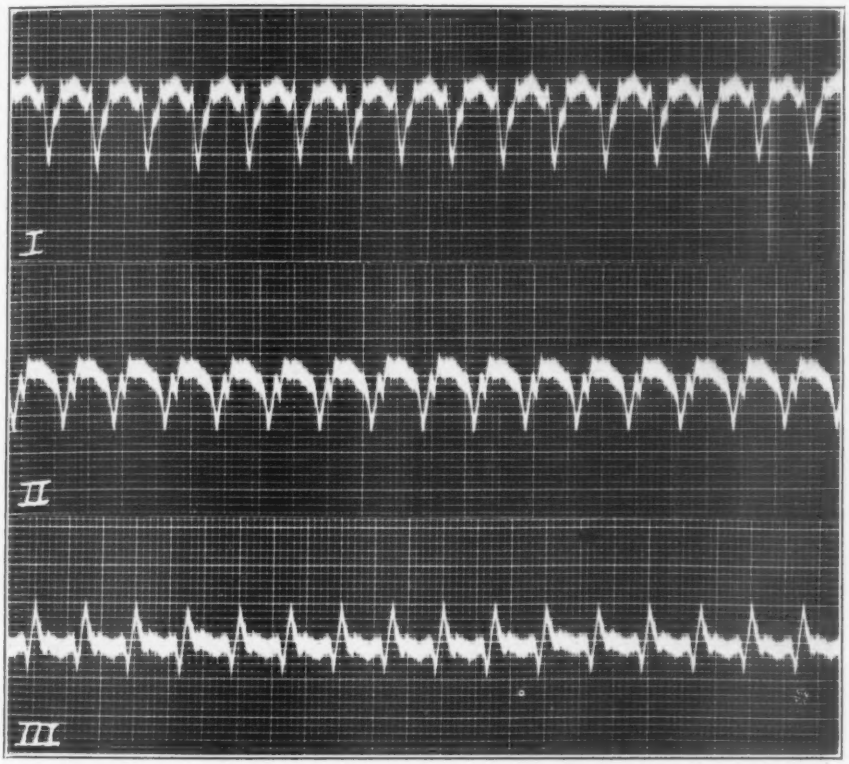

Fig. 1.—Sept. 22, 1930. Paroxysmal tachycardia, probably auricular. Rate 200. ? P-waves Lead III. QRS = 0.12 sec., slurred in all leads. T opposite main deflection in all leads. Right bundle-branch block (if tachycardia is auricular in origin.)

symptoms. During the next few weeks, his congestive failure cleared, and he was discharged in apparently good condition four and a half weeks after his return to normal cardiac rhythm.

On April 4, 1931, five months after discharge, he was readmitted to the hospital acutely ill. Following his first discharge from the hospital, he had been able to return to work and had been without symptoms until a few hours before his readmittance. He entered the hospital in a condition of shock. The temperature, by mouth, was 96 degrees Fahrenheit. The pulse rate was 65 per minute. The respirations were 30 per minute. The white blood count was 20,000 per cubic millimeter of blood. He lived only six hours following admission to the hospital.

Post-mortem Examination of Heart.—The weight was 360 gm. The organ was essentially normal in size. The epicardium was smooth but showed slight discoloration over the posterior portion of the left ventricle. The myocardium was pale greyish red in color and was markedly scarred. Immediately below the mitral ring, extending posteriorly as far as the interventricular septum, and inferiorly as far as the apex, there was a pear-shaped area approximately 5 or 6 cm. in diameter where the myocardium was thinned, mottled yellowish grey in color, containing hyalin appearing bands; the thickness at this point was 0.7 cm. The valves were negative with the exception of slight atheroma of the aortic. The aorta immediately above showed marked thickening of the intima, with the formation of plaques and nodules some of which were yellow in color and appeared atheromatous; others were bluish in color and hyalin in appearance, giving the appearance

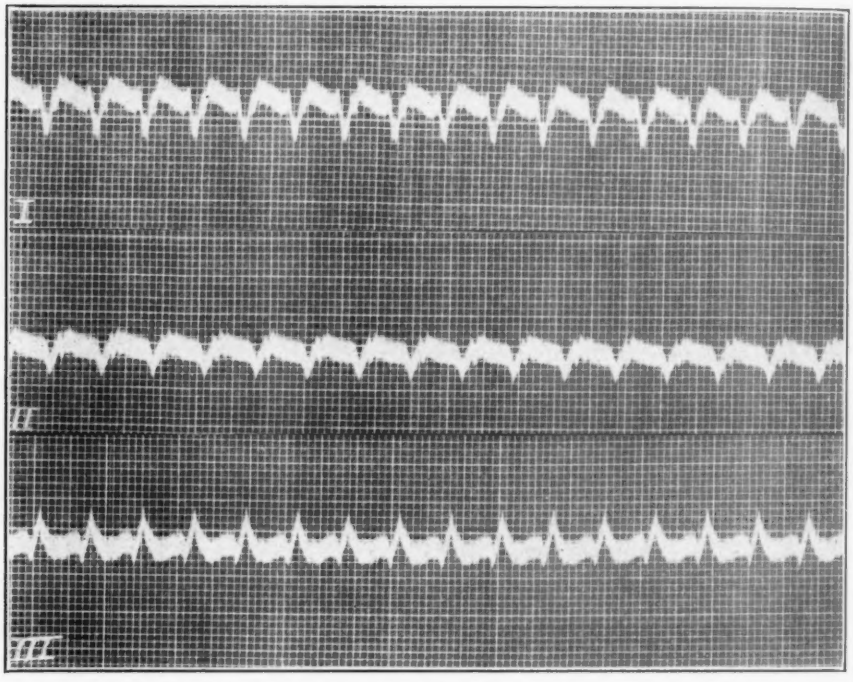

Fig. 2.—Oct. 10, 1930. Paroxysmal tachycardia, probably auricular. Rate 200. ? P-wave Lead III. QRS = 0.12 sec. slurred in all leads. Right bundle-branch block (if tachycardia is auricular in origin). Low amplitude (maximum 5 mm.).

of syphilis. The mouths of both coronaries were patent but thickened. The right coronary at the level of the tricuspid valve showed almost complete occlusion. The vessel at this point was yellowish grey in color and appeared hyalinized. Beyond this point the lumen was patent but very narrow. The interventricular portion of the left coronary about 2.5 cm. from its point of origin showed an occlusion by a red, soft thrombus; beyond, the vessel wall was thickened but patent. The circumflex branch of the left coronary 1 cm. from its point of origin showed complete occlusion, from an old process. The healed infarcted area described above lay below.

During the patient's stay in the hospital, he was under the care of Drs. L. B. Ellis, B. E. Hamilton, D. Hurwitz, W. R. Ohler, W. H. Robey, and F. W. White. The electrocardiograms were taken and interpreted under the direction of Dr. J. M. Faulkner. The post-portem examination was made by Dr. J. M. Woodall.

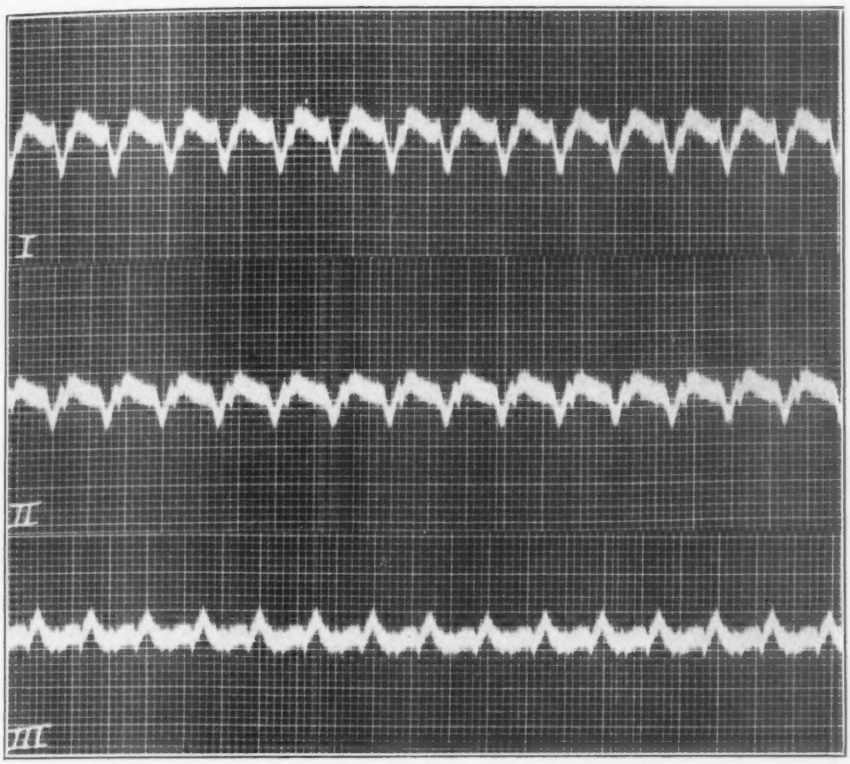

Fig. 3.—Oct. 18, 1930. Paroxysmal tachycardia, probably auricular. Rate 200 ? P-waves Lead III. QRS = 0.12 sec., slurred in all leads. T opposite main deflection in all leads. Right bundle-branch block (if tachycardia is auricular in origin). Low amplitude (maximum 4.5 mm.).

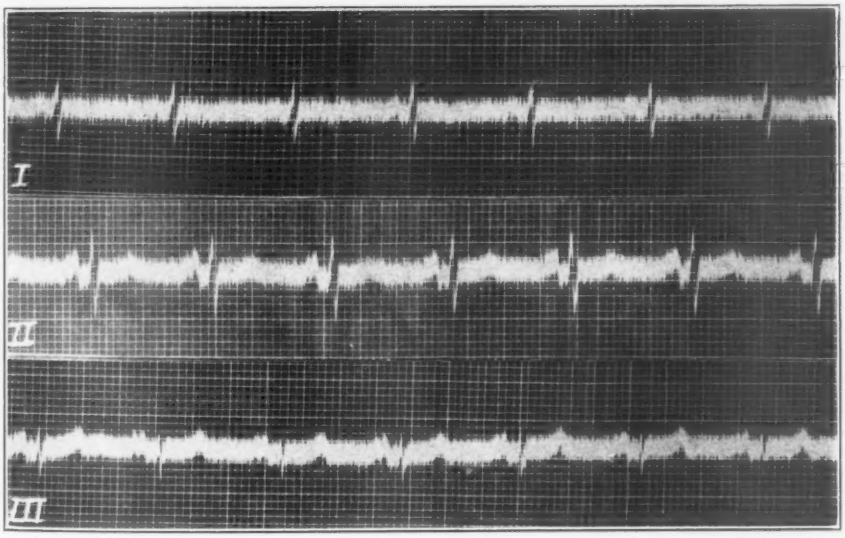

Fig. 4.—Nov. 20, 1930. Normal sinus rhythm. Rate 94. PR = 0.12—0.14 sec. QRS = 0.06 sec. T^1 inverted, T^2 T^3 upright. Axis normal. Low amplitude (maximum 5 mm.).

COMMENT

The important findings are:

1. *Duration of paroxysmal tachycardia.*—Though it is known that paroxysmal tachycardia may continue indefinitely, a duration of more than a few days is rare and very few cases have been reported with a known duration of thirty-five days with recovery. The attack may have been present during the two weeks before admission, making a possible total of forty-nine days.

2. The patient was not conscious of his tachycardia. He complained only of gastrointestinal disturbance.

3. The paroxysmal tachycardia was probably associated with a coronary occlusion with infarction. This was indicated by the subsequent post-mortem examination. There was no clinical evidence to confirm this diagnosis, except the unexplained paroxysmal tachycardia itself. The gastrointestinal discomfort might have been the result of the paroxysmal tachycardia alone. So far as is known, this is the first and only attack of paroxysmal tachycardia that the patient had.

4. Digitalis and quinidine sulphate by mouth and digalen intravenously were not followed by any appreciable change in rate. Quinidine sulphate intravenously caused a reduction in rate for twenty minutes only. Quinine hydrochloride by mouth was accompanied by some slowing of rate and a return to normal rhythm.

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